3 6

SCIENCE

MARCH 14, 1952

VOLUME 115 NUMBER 2985

Contents

Insects as Experimental Material: *Kenneth D. Roeder* 275

News and Notes

European Congress of Nobel Prize Winners in Medicine: *William P. Murphy* 280

Technical Papers

Charge Distribution in Nuclei from X-Ray Fine Structure: *A. L. Schawlow* and *C. H. Townes* 284

An Artificial Kidney—A Simplified Apparatus: *John R. Guarino* and *Louis J. Guarino* 285

Blood Factors in the Nutrition of *Trypanosoma cruzi*: *W. L. McRary, E. R. Noble,* and *E. L. Tondevold* 288

The Archaeological and Paleontological Salvage Program at the Medicine Creek Reservoir, Frontier County, Nebraska: *E. Mott Davis* and *C. Bertrand Schultz* 288

Antagonistic Action of Uracil, Thiouracil, and Thiourea on Reticulocyte Ripening: *Alphonse Nizet* 290

Some New Synthetic Estrogens: *H. Rinderknecht* and *L. W. Rowe* 292

Comments and Communications

"Attraction Fields" between Growing Tissue Cultures: *Paul Weiss* and *Allan A. Katzberg* 293

Root-Grafting in Tropical Trees: *Carl D. LaRue* 296

Separation of Free-Living Cells: *Robert G. H. Cormack* 296

Scientific Research in Australia 3

Meetings & Conferences 16

Publications Received 18

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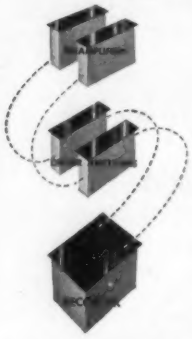

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Scientific Research in Australia

AUSTRALIA, settled only since 1788 and an independent nation since 1901, has faced development problems arising largely from these circumstances, which are in many respects unique. The environment confronting the first settlers was so vastly different from their past experience that old methods had to be replaced by new ones evolved from relatively fundamental principles. Agriculture was naturally the prime problem; there was no native agriculture and hence no guide to what crops and practices suited local conditions. The soils, climate, vegetation, and fauna were quite dissimilar from those in Britain. Many problems have not yet been satisfactorily resolved, and research in agriculture and biology is still vitally important to the country.

Research for these "primary" industries was given a prominent place when the new dominion initiated research activities following federation in 1901; and from small beginnings, as the Institute for Science and Industry, grew the federal government Council for Scientific and Industrial Research, established by act of Parliament in 1926. In 1949, the council, in turn, became the Commonwealth Scientific and Industrial Research Organization.

Meanwhile, two world wars, in which the Commonwealth of Australia was a full participant, stimulated progressively more emphasis on research in the physical and engineering sciences, which are now strongly represented in this and other Australian institutions. The greater part of CSIRO's activity is, however, still focused upon the fundamental aspects of agriculture and biology. Set up along lines similar to the Department of Scientific and Industrial Research in the United Kingdom, CSIRO now includes 34 separate research units spread over the nation, of which 20 are concerned mainly with the primary industries. (There are 15 major divisions, 14 independent sections, and 5 regional laboratories, the last having diversified staffs and each of the others having one or more specialized laboratories and field stations.)

Only two well-known research projects in which CSIRO has been prominent will be mentioned: Noteworthy progress has been made in elucidating the parts played by several of the minor elements in plant and animal nutrition. Since Australia has large areas in which soils are deficient in one or more of these elements, this has already resulted in marked increases in production and in better land utilization. Even some former wastelands are now in use. The second project is the development of aids to navigation that have won world-wide recognition and acceptance. These are typical of the scientific projects in the civil field directed toward the development and use of the nation's resources. The organization's budget is now about £A3 million ($6.7 million), which is considerable for a country with an area substantially the same as that of the United States but populated by less than nine million people.

The demands of World War II led to extraordinarily fast growth in industry, and this has continued under the stress of conflict in Korea and world economics. These factors have caused other research agencies to grow rapidly, too. The joint venture Australia is making with the United Kingdom into the development and testing of long-range guided missiles, together with other less spectacular defense programs, has given prominence to the contributions made by the other two major scientific agencies of the federal government, the Defense Research Laboratories and the Aeronautical Research Laboratories of the Department of Supply.

The remaining foci of research are the universities. Until recently there were six, one in each state, but independent of government in management. Recently New South Wales has established a University of Science and Technology, and the federal government the Australian National University in Canberra, an institution of higher learning devoted to research at a high level, and not primarily to teaching. Through the National University such outstanding Australian scientists as Howard Florey and Marcus Oliphant are again being linked closely with Australia.

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SCIENCE, founded in 1880, is published each Friday by the American Association for the Advancement of Science at the Business Press, 10 McGovern Ave., Lancaster, Pa. Entered as second-class matter at the Post Office at Lancaster, Pa., January 13, 1943, under the Act of March 3, 1879. Acceptance for mailing at the special rate postage provided for in the Act of February 28, 1925, embodied in Paragraph (d-2) Section 34.40 P. L. & R. of 1948.

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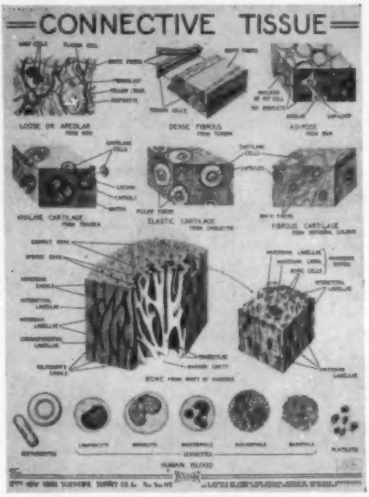

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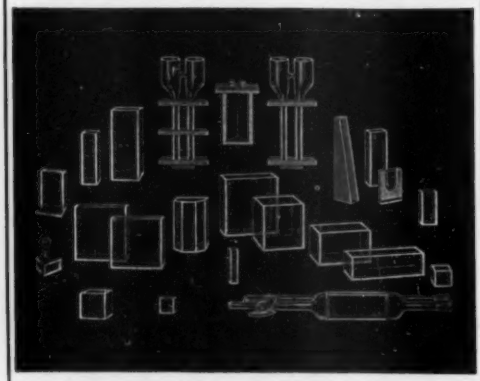

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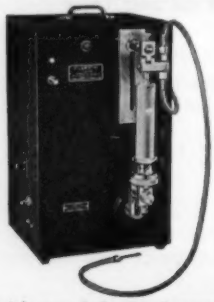

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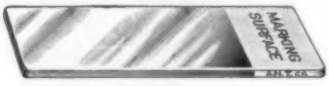

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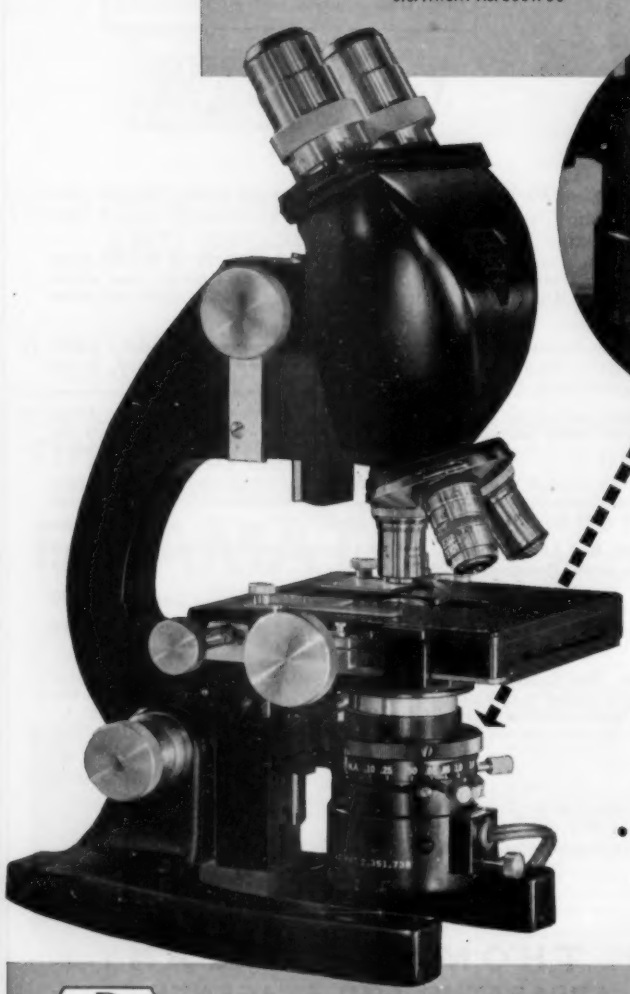

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Tufts College, Medford, Massachusetts

INSECT PHYSIOLOGY APPEARS to be passing from a phase of very rapid and often disconnected expansion into one of steady growth. Although certain isolated segments of the field were studied intensively as much as fifty years ago, the sudden expansion of the past ten to twenty years is due to an influx of many investigators from other fields. The latter have brought to the study of insect function new intellectual and physical techniques, with the result that many of the gaps have been filled and insect physiology may now be said to have some degree of organization.

Coherence in insect physiology owes much to the work of V. B. Wigglesworth who, in 1939, published the first textbook (*1*) on the subject. The recent or imminent appearance of two other books dealing with insect function as a whole (*2, 3*) will bring about further integration. Although this transition is inevitable and most valuable in any field, it should be borne in mind that insects operate on the same basic principles as the rest of living matter, and that the study of insect function is not an isolated category of knowledge with its own methods and sphere of operations. The insect physiologist recognizes that insects are in many ways peculiarly suited to the physiological approach and, in presenting his findings, recommends them as research material to other physiologists. At the same time, he shares with insect taxonomists and morphologists an interest intrinsic to insects as a group. Finally, his relations to economic entomology are comparable to those of other physiologists to medicine, the applied science often bringing to light the problems of greatest interest.

The late start of insect physiology can be traced to several causes. The phylogenetic position of insects as a specialized class, well removed from the main stem of vertebrate ancestry, may have been responsible for the feeling that analysis of insect function would add little to general physiology. Nonetheless, the basic principles of general physiology presumably apply to all forms of life, and the fact that in insects they may appear in a highly specialized form or application frequently makes them more amenable to experimental analysis. Furthermore, the small size of most insects has undoubtedly deterred many a physiologist accustomed to the frog, rat, and dog. However, modern analytic and recording techniques have largely overcome difficulties of chemical analysis and registration of responses; the problems of dissection and manipulation do not constitute major obstacles and can usually be met by mechanical devices and by practice. Actually, the small size and short life cycle characteristic of most insects turn out to be advantageous, since they greatly increase the ease of culturing and sampling of large populations, a fact long recognized by geneticists in their studies of one of the smaller flies (*4*).

The fact remains that the class Insecta contains a larger number of species with a wider distribution than all the rest of the Metazoa. Like their main competitor, man, many genera of insects are of recent origin, their state of evolutionary flux being indicated by the confusion of subspecies, varieties, and mutations, which plague the systematists and economic entomologists and delight the geneticists.

It was the original intent of this article to present a picture of the status of insect physiology. A first attempt in this direction produced merely a list of generalizations and a realization that the subject was already far too large and fluid to submit to a short summary of its status. Accordingly, only a few of the mechanisms by which insects maintain relations with their environment—muscles, nerves, sense organs, and behavior—are used here to illustrate present trends in insect physiology. Equally good examples can be found elsewhere in studies of the cuticle (*5*), the structure that most nearly characterizes arthropods, the intensive work in many laboratories on the hormonal control of molting and metamorphosis of insects, and the peculiar adaptations of insects to aquatic respiration (*6*). For these, and for recent work on respiration, blood, osmoregulation, digestion, and developmental physiology of insects, the general references given above and papers by Wigglesworth (*7–9*) should be consulted.

Examples

Insect flight. The wings of insects, unlike their analogs in other aerial animals, appear to have arisen solely in connection with flight and not from preexisting locomotor appendages. During flight the shape of the thorax is altered by the contraction of two massive sets of muscles within, the movement being transmitted to the wings by a hinge mechanism. Flight may be studied in suspended insects, which can be made to beat their wings by removing a platform from beneath their feet. Wing-beat frequencies of several hundred per second are commonplace among flies, *Drosophila* being capable of continuous flight for 1½ hours, during which the wings may beat 1½ million times (*10*).

In the course of such a flight, *Drosophila* may de-

plete glycogen reserves to the extent of 3.5 per cent of its body weight (*10*). The extraordinary speed at which metabolic reserves are mobilized during this drastic expenditure of energy is shown by the observation that an exhausted *Drosophila* is able to resume flight 45 seconds after drinking a glucose solution, 1 μg of glucose maintaining flight for 6.3 minutes (*11*). The extent of the energy expenditure during flight may be judged from the oxygen consumption, which may be as much as fifty times that of the resting insect (*12, 13*). Little is yet known of the mechanisms of oxygen transfer and heat dissipation or of the systems of metabolic enzymes associated with such prodigious activity, although large numbers of sarcosomes containing enzymes in concentrated form are present in the flight muscles of those insects with the highest wing-beat frequencies (*14*). It is also significant that the oxidation and reduction of cytochrome were first observed (*15*) in the flight muscles of a moth. Analyses of the aerodynamic efficiency and power output of flying insects (*16*) should be of immense value when they can be fully correlated with metabolic studies.

There are several reasons why insect flight should provide valuable information on the energetics of muscular performance. First, flight represents a level of activity entirely natural to the organism, and may be repeatedly started and stopped without recourse to artificial stimulation. Second, the work done in terms of air moved takes the form of a continuous output and, in spite of the magnitude of the metabolic expenditure, may be maintained at a steady level for an hour or more. Third, in the movement of the wings we see a repetition of the pattern of cyclic change or oscillation that is almost universal in living systems. Compared with activity such as the heartbeat, sexual cycle, or cortical rhythms, insect wing movements occur at a very high frequency, show all degrees of departure from a simple linear oscillation, and may be experimentally modified in both these parameters (*17*). It is suggested that these characteristics should make flight movements more accessible to analysis than most types of oscillation found in biological systems.

Insect flight raises many interesting questions of nerve and muscle function. The thorax of the higher insects is almost completely occupied by two sets of flight muscles, which contract at right angles to each other to alter the shape of the elastic thorax and thereby to move the wings. The frequencies at which this takes place range from 5 wing beats per second in butterflies to several hundred per second in many flies. The latter figure differs by a factor of ten from the most rapid muscle performance of vertebrates. In cockroaches, grasshoppers, dragonflies, moths, and butterflies, wing-beat frequencies are generally below 60 per second, and each contraction of the flight muscles appears to be due to a nerve impulse from the central nervous system. This, in principle, is similar to the mechanism of striated muscle excitation in other groups of animals. In flies, wasps, and beetles, in which much higher frequencies generally (although not invariably) prevail, there may be 2–40 wing beats to each motor nerve impulse. Furthermore, impulses and wing beats are not synchronized; irregular bursts of potentials precede wing movement by as much as 50 milliseconds and cease a similar period before flight is actually terminated. The current explanation (*18, 19*) for this lack of synchronism is that the nerve impulses build up in the muscle pair a state of instability that eventually leads to oscillation. Oscillation is directly maintained by the tension developed in one muscle through the contraction of its antagonist; this in turn causes it to contract and develop tension in the antagonist. The oscillation of the muscle pair tends to become damped by the transfer of energy via the wings to the surrounding air, an effect which is offset during flight by the conditioning action of the irregular sequence of nerve impulses. Damping becomes apparent at the end of a flight as the whole apparatus coasts to a stop some time after the cessation of nerve impulses. Although details of its operation are still lacking, it is clear that this excitatory system obviates the need of maintaining during flight a sequence of nerve impulses at several hundred per second.

Insect ganglia and nerves. Insects have much to offer as experimental material for studies of nerve action. Metameric separation of the ganglia composing the brain and nerve cord is reflected in a considerable degree of autonomy of ganglion function. The arrangement of insect ganglia is reminiscent of the autonomic ganglia of vertebrates, although the former are concerned with locomotion and other somatic reflexes and, consequently, are more complex. The small size of insect ganglia and nerves introduces certain difficulties in connection with electrical stimulation and recording, particularly where this concerns the characteristics of conduction in axones. However, individual nerve fibers are often of considerable diameter, reaching 50 μ in certain internuncial fibers of the cockroach. From this it follows that the total number of neurons composing the nervous system is relatively small, many of the muscles being supplied by only one or two motor fibers. This makes it possible to observe central nervous activity in terms of single fiber responses without the necessity for actual isolation of the fibers involved (*20*). In general, insect synapses have similar properties to those of vertebrates, synapses of widely differing degrees of complexity or lability being obtainable in the same preparation (*21*). Cholinesterase is present in ganglia in considerable quantities (*22, 23*) and appears to play an essential role in synaptic conduction. Acetylcholine is also present in large quantities, although the part it plays in nerve activity is not clear. The pharmacology of the insect central nervous system presents interesting parallels and contrasts with vertebrates. Anticholinesterases have rather similar actions on synaptic conduction in both groups, whereas acetylcholine, atropine, curare, and strychnine have little or no action upon central or upon neuromuscular junctions in the cockroach (*24*).

Spontaneous nerve activity. This somewhat ill-defined term is used to designate activity occurring in excitable tissue after it has been completely separated from its normal nervous connections and sense organs. Twenty years ago Adrian (*25*) detected an irregular but sustained series of nerve impulses in the completely isolated ventral ganglia of a caterpillar. Since then spontaneous activity has been studied extensively in the isolated nervous systems of the crayfish (*26*) and cockroach (*27*), although its significance as a form of nerve activity is still uncertain. Many insect sense cells, as well as central neurons, discharge repetitively even under conditions approaching zero stimulation. This suggests that spontaneous activity constitutes not only a form of residual tonus when external stimuli are at a minimum, but also a means for greatly extending the sensitivity of excitable cells. A spontaneously active neuron may be said to lack a finite threshold, since it must sweep from a very high threshold (refractoriness) during discharge to zero threshold (excitability by thermal noise) when it reaches the point of spontaneous discharge (*28*). External stimulation imposed upon this rhythm could be effective from very high, down to very low, levels, triggering the discharge either earlier or later in the cycle and modulating the frequency of the rhythm. The significance of spontaneous activity in sensory and central neurons has not yet been fully appreciated, although it finds a place in the concept of endogenous activity as a factor in innate behavior (*29*).[1]

Sensory physiology. The relative fixity of their behavioral patterns under experimental conditions and certain peculiarities of their sensory equipment make insects eminently suitable for many types of experimentation in this field. In flies and in many other insects the taste chemoreceptors are found upon the feet, as well as the mouth parts. Application to the feet of an acceptable (e.g., sweet) solution brings about extension of the proboscis into the drinking position, whereas an unacceptable solution (e.g., acid, distilled water) causes no drinking response, provided the insect has been allowed previously to drink distilled water ad libitum. The taste threshold for an acceptable substance may be measured by noting the apearance of the proboscis response when the feet of the insect are dipped successively into progressively greater concentrations of the test substance, which the insect is prevented from drinking. The rejection threshold is measured in a similar manner, the feet being dipped into a series of solutions that contain a fixed and acceptable concentration of sugar, together with various concentrations of the test substance. The unacceptability of the substance is measured in terms of the concentration which just extinguishes the proboscis response to the sugar. This technique has made it possible to measure the rejection thresholds of blowflies for extensive homologous series of various alcohols, fatty acids, aldehydes, and ketones (*30*), permitting for the first time an evaluation of the relation between stimulatory effectiveness, length of carbon chain, and colligative properties of organic compounds (*31*). In addition to the invariant nature of the proboscis response, the fact that blowflies may be raised (2 weeks per generation) and handled by simple methods (*32*) in tens of thousands in the space of the average laboratory has contributed much to the scope and statistical reliability of these studies.

The location of chemoreceptors in groups upon the feet suggests experiments with this sense in insects which could not be carried out with forms in which the taste organs were either diffusely distributed or limited to the oral surfaces. In nutritional and metabolic studies an insect may be induced to drink tasteless or normally rejected solutions by dipping its feet into a sugar solution (*33, 34*). Adaptation, summation, and inhibition in peripheral and in central neurons may be investigated by dipping various numbers or combinations of legs into various concentrations of a test solution, or by dipping one leg into an acceptable, and another into an unacceptable, solution. Temporal factors in central nerve activity can be examined by applying to one leg a conditioning stimulus and to another a test stimulus (*35*).

Although the olfactory and humidity senses have not been so intensively studied, insects are promising material in this direction also. Not only do they show well-defined taxic responses to odors (*36*) and water vapor (*37*), but the sense cells concerned in these responses are located on the antennal surfaces and hence are quite accessible. The size of the antennae of many insects suggests sensory nerve fibers of considerable length, a desirable condition for examination of the afferent nerve response to chemical stimulation of the sense cells.

The reproducibility of the phototaxic responses of insects in a laboratory situation has been responsible for a considerable volume of published work on intensity, flicker, form, and color discrimination (*1–3, 38*). The optics and anatomy of the compound eye also received much attention from early investigators. In spite of its complexity, the compound eye is much less efficient as an optical instrument than is the eye of vertebrates, although recent work has shown that it possesses two attributes that are of special interest to students of behavior and may be more widely distributed than heretofore realized. An examination of the electroretinogram of honeybees shows that these insects may be able to discriminate individual pulses produced by a flickering light, or by a pattern when moved relative to the eye, even when the pulses occur at frequencies as high as 300 per second (*39*). This is clearly of value to an organism moving at a high angular velocity with respect to its surroundings. Honeybees are able to utilize the polarization pattern of light refracted from the sky as a fixed point in their route-finding and orientation (*38*). Ants show a similar ability to discriminate the plane of polarized light (*40*), and the retinulae of another arthropod, the horseshoe crab, appear to be individually oriented to a particular plane of light polarization (*41*).

[1] See also TINBERGEN, N. *The Study of Instinct.* Oxford, Eng.: University Press (1951).

In the domain of the mechanical senses, hearing is well developed in many insects (*42*), although insect auditory organs probably never achieve the resolving power of the mammalian ear. The semirigid cuticle imposes special conditions on the sense organs of touch and of the position of body parts. Hinged spines serve as tactile organs, and groups of fine hairs on the cuticle are bent by the movement of one component of a joint upon the other. Torques and shearing forces developed in the cuticle by gravity or by resistance to movement are transduced into nerve impulses by groups of dome-shaped campaniform organs (*43*). A striking example of the function of campaniform organs is seen in the halteres of flies. Each haltere, a modified hind-wing, consists of a short shaft surmounted by a knob. During flight, muscles keep the haltere in oscillation at wing-beat frequency in a fixed plane with respect to the body axis. Any tendency of the flying insect to yaw or pitch causes in the cuticle at the haltere base a gyroscopic torque which stimulates campaniform organs in this region and initiates reflex corrective movements of the flight muscles (*44*). Thus the fly is provided with a gyrocompass.

Behavior. Insects have long been favorite subjects for the study of behavioral mechanisms, particularly those concerned with social activities. Their small size and relatively small radius of activity permit the unbroken observation of a complete behavioral sequence such as foraging and feeding, courtship and mating, and the like. In addition, the relative fixity of many of their taxes is undoubtedly responsible for the fact that more is known about the quantitative relation between physical and chemical gradients and orientation in insects than in other animal groups (*45*).

It is well known that the anthropomorphic interpretation of observations is one of the commonest sources of error in behavioral studies of animals. However, it seems to be just as erroneous to evaluate the responses, learning capacity, and memory of the subject when it has been observed only in a man-made environment, as it is to attribute to it human tendencies and desires. The casual observer becomes acquainted with the behavior of an insect such as a bee in the artificial environment of a windowpane or a restraining box, where its activities frequently consist of random seeking movements or invariant orientation with respect to some one environmental gradient such as light. Under circumstances for which its sensory and motor equipment is ill-adapted, one sense modality, usually vision, appears to dominate its activity, and the insect exhibits little capacity to modify its behavior on the basis of experience gained in moving about in this artificial environment. If the sensory equipment of an organism is considered to be adapted to its normal environment, there must be some degree of equivalence of the various sense modalities, and the fact that one sense frequently dominates the actions of insects in an experimental situation must be taken as a sign of sensory and therefore of behavioral imbalance, even though it may be a characteristic of great value in studies of sensory function. By this it is not meant that laboratory studies of insect behavior are dispensable; merely that they will gain greatly in significance if repeatedly related to the natural environment of the subject. This viewpoint is confirmed by the following examples.

There have been a number of studies of the ability of cockroaches (*46*) and ants (*47*) to learn and to remember a maze habit. In learning this type of task insects require a great many more trials and retain a memory trace for a much shorter time than most vertebrates (*47*). On the other hand, solitary wasps have shown a striking capacity to learn the topography of their nesting and foraging region, being able to reorient themselves almost immediately when transported to another part of it in a dark box (*48*). Perhaps the most startling evidence of learning and communication by insects is to be found in the beautiful work of von Frisch (*38*). A worker honeybee returning to the hive from a rich source of food not only remembers and is able to retrace its path, but can communicate to other workers both the distance and the direction of the source of nectar. When surrounded by hive mates the returning bee performs a series of movements—the "waggle dance" of von Frisch—in which the speed of movement in one phase is inversely proportional to the distance of the food, and the direction taken in another phase of the dance indicates the direction of the food. The reference point both for the foraging trip and for the subsequent symbolic indication is the sun, or if this is not visible, the pattern of polarized light refracted from the sky. When the dance is performed in the darkness of the hive where neither of these reference points is available, the bee, dancing on the vertical surface of the comb, transposes the effects of light into those of gravity, moving at an angle with the vertical which is identical with the angle formed by the food source, hive, and sun. After repeating this dance the recipient bees leave the hive, and, transposing their movements once more into distance and direction, fly directly to the source of nectar.

Communities of many ant species are as complex and well organized as that of the honeybee, although the principles underlying group coherence and communication are still not too well understood. We owe to the brilliant studies of Wheeler (*49*) the important suggestion that group integration is based upon the exchange of regurgitated food material between the members of an ant colony. This concept of trophallaxis finds support and further development in investigations on army ants (*50*), whose colonies pass through regular cycles in which a nomadic phase alternates with a passive phase. The key to this group behavior is found in the condition of the developing broods, which as larvae furnish a maximal stimulative (tactual and chemical) effect on the population, maintaining a nomadic condition in the colony, and as enclosed pupae furnish only a minimal stimulative effect.

These few examples serve to illustrate the complex behavior of insects under different circumstances—an invitation to further research.

Practical Considerations

The work described in the preceding pages is a small segment of the field, chosen frankly because it is of particular interest to the writer. However, it serves to illustrate the general trend and vigor of insect physiology. Although this vigor is obviously dependent upon the intellectual caliber of investigators attracted to the study of insect function, there are other less obvious but equally important reasons for present activity in the field. The explosion of the atomic bomb performed a great service by largely eliminating the classical distinction between the "pure" and "applied" sciences. At about the same time industrial research introduced DDT, an insecticide unsurpassed at that time for its high toxicity to insects and low toxicity to mammals. These events appear to have convinced many concerned with the economic relations of insects to man that (1) a reasoned approach and an understanding of the operation of natural phenomena might in the long run provide more effective means for insect control than the mere empirical testing of insecticides and (2), since DDT showed a selective toxicity to arthropods, an understanding of its mode of action should make possible the development of insecticides toxic only to certain species of insects and even less toxic to man and domestic animals.

Thus insect physiology received a certain degree of moral and practical support. In the United States the Office of Scientific Research and Development was one of the first agencies to implement this attitude during the closing year of the war by contractual research, mostly relating to the mode and site of action of DDT. At the same time, several other agencies, notably the Army Chemical Corps, Quartermaster Corps, and the Public Health Service, farsightedly realized that, although their interests in insects and chemical action were of a purely practical nature, the surest way to achieve their objectives was to support studies of insect function in which the development of new insecticides was incidental. This support has continued, and at the present time the Army Chemical Corps has one of the finest laboratories in insect physiology in the United States in its Entomological Division at Edgewood, Maryland. In addition, this and other agencies support university research in insect physiology by means of contracts. Many of the state agricultural stations with their rather similar objectives are taking a comparable interest in insect function.

The intelligent attitude of these supporting agencies has eliminated much of the proverbial distrust of university workers for sponsored research, and has brought about a natural fusion of the objectives of the two groups. For instance, determination of the gustatory and olfactory thresholds of flies in relation to the structure and properties of the stimulating compounds (*30, 31*) has certainly enlarged our knowledge of this branch of sensory physiology, and at the same time suggests a rational basis for the synthesis of specific insect attractants and repellents (*36*). Work begun with the practical object of determining the site and mode of action of agents such as DDT, diisopropyl fluorosphosphate, and hexaethyl tetraphosphate has also supplied information on sensory function (*51*), ganglionic activity, and the chemical factors in synaptic conduction in insects (*22–24*). Similarly, a knowledge of the energetics of flight (*16*) and of the behavioral mechanisms of insects (*50*) is clearly prerequisite to a rational understanding of insect migration and distribution, although these topics have an obvious intrinsic importance. Similar examples are to be found in work on the cuticle, metabolism, biochemistry, and developmental physiology of insects (*1–3, 5*).

At the present time great interest centers around the appearance in the field of strains of houseflies and mosquitoes highly resistant to DDT. This situation can be duplicated in the laboratory (*52*) when flies are subjected to the selective action of DDT for five to eight generations. The structural and functional modification conferring resistance to DDT has not yet been detected, but this practical problem offers ideal experimental material for a study of the changes that form the basis of natural selection. From the physiological viewpoint alone, the problem stretches all the way from the ultrastructure, chemistry, and physical properties of the cuticle (*5*) as the point of entry of DDT, to the properties of the excitable tissue affected and the nature of the enzyme systems basic to metabolism and excitability. Solution of this problem will fill many gaps in our knowledge of the physiology of insects, as well as provide a highly significant contribution to human health and welfare.

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News and Notes

European Congress of Nobel Prize Winners in Medicine

THE first European Congress of Nobel Prize Winners in Medicine was held in the town of Lindau im Bodensee June 10–14, 1951. The object of the congress was to provide a program of sufficient scientific interest and practical value to attract physicians from all parts of Germany and from neighboring countries, to meet for the purpose of stimulating a renewed interest in scientific medicine and a more congenial personal relationship. The congress was arranged by a committee of German physicians and citizens under the leadership of Karl Hein and Professor Parade, and under the protectorship of Prince Lennart Bernadotte of Sweden, whose summer home is on the Isle of Mainau im Bodensee. It is the intention of the committee to make the congress an annual event.

The scientific entertainment for the 500 physicians and their wives who attended the congress was provided by addresses presented by the Nobel prize winners, who summarized and brought up to date the work for which the prize was awarded. Addresses were given by G. Domagk, of Wuppertal, Germany; P. H. Müller, of Basel; H. Dam, of Copenhagen; A. Butenandt, of Tübingen; O. Warburg, of Germany; and W. P. Murphy, of Boston, Mass. H. von Euler, of Stockholm, a prize winner in chemistry, also attended the meetings.

In his opening address before the congress Dr. Hein stressed the acute lack of contacts among scientists in Germany and other countries since 1933 and the consequent lack of interest in, and incentive to carry on, scientific investigation, or to use the newer methods in practice. Dr. Hein felt that renewed interest and incentive should follow upon reports of their own investigative work, by men of outstanding achievement in science from various countries.

The success of the congress was evident from the attendance and the active interest in each of the papers presented. It is the intention of the committee to invite, in rotation, as guest speakers for future congresses, the prize winners in the several fields for which Nobel established an award.

The success of future meetings should be assured by the place of meeting, the social entertainment apart from the scientific programs, and the courteous treatment accorded the guests of honor. Lindau is an interesting old city, situated on an island in the Bodensee (Lake of Constance) in Bavaria. In addition to several sight-seeing trips for the ladies, there was an evening of ballet, a dinner at Hotel Bad Schachen, which overlooks the beautiful Bodensee where the Rhine enters the lake, and an all-day steamer excursion to Meersburg Castle, the interesting island estate of Prince Lennart, and other points of interest.

WILLIAM P. MURPHY

Boston, Massachusetts

Scientists in the News

Dana K. Bailey, of the National Bureau of Standards Central Radio Propagation Laboratory, has received the Arthur S. Fleming Award as the outstanding young government man of the year. The award is given annually by the Washington (D. C.) Junior Chamber of Commerce. Mr. Bailey received the award for his contributions in the field of radio wave propagation, and for his extensive service in the field of international relations. Since 1948 he has been a U. S. technical representative at a number of meetings of agencies of the International Telecommunications Union.

The University of Maine Pulp and Paper Foundation presented **George D. Bearce,** of Bucksport, Maine, its 1952 Honor Award "in recognition of outstanding service to the pulp and paper industry in management

and technology." Mr. Bearce is general manager of St. Regis Paper Company operation in the state of Maine.

William M. Cook, Jr., has been appointed manager of Canadian operations for Vick Chemical Company. Mr. Cook formerly was assistant product manager of the Sofskin Company, a Vick subsidiary.

Earl G. Droessler has been made executive director of the Committee on Geophysics and Geography, Department of Defense Research and Development Board. Mr. Droessler has served as staff meteorologist, ONR, since 1946, and most recently was head of the ONR Meteorology Program in the Geophysics Branch of the Earth Sciences Division.

Fred J. Emmerich, president of Allied Chemical & Dye Corporation, New York, has been awarded the 1952 Gold Medal of The American Institute of Chemists. The award was made in recognition of Dr. Emmerich's achievements "as a business leader devoted to building chemical industry by fostering cooperation among men skilled in chemistry, engineering, and commerce." The medal will be presented at the annual meeting of the institute, to be held in New York May 7–8.

Thomas F. Farrell, assistant general manager of the U. S. Atomic Energy Commission since August 1951, has resigned to become managing director of ARO, Inc., which manages and operates the Arnold Engineering Development Center at Tullahoma, Tenn.

After 43 years of service on the board of directors of Morningside Sanatorium, Madison, Wis., **William D. Frost,** professor emeritus of bacteriology at the University of Wisconsin, has retired as president of the organization, which he helped found and build. He has consented to remain as consultant to the medical director at Morningside. For more than half a century, Dr. Frost has been a leader in the local, state, and national crusade against tuberculosis.

George Gamow, professor of theoretical physics at George Washington University, will go to Japan in May for a three-week lecture tour, as one of four international figures invited by *Asahi,* Tokyo newspaper, to participate in the Japanese Peace Treaty celebrations. The others are **J. B. Priestley,** British novelist; **Leon Jouhaux,** French winner of the 1951 Nobel peace prize; and **Eleanor Roosevelt.**

James K. Holloway, biological control specialist, University of California Agricultural Experiment Station, will spend a year in Mediterranean countries searching for parasites of the leaf hopper, which spreads curly top, a serious virus disease of tomatoes, sugar beets, and several other major crops in California's San Joaquin Valley. The project is sponsored jointly by the USDA and the University of California.

E. G. McKibben has been named director of agricultural engineering research in the Bureau of Plant Industry, Soils, and Agricultural Engineering at Beltsville, Md. Dr. McKibben has been in charge of the department's Tillage Machinery Laboratory at Auburn, Ala. His appointment fills a vacancy left by the death last fall of **Arthur W. Turner.**

Three members of the National Research Council of Brazil visited the National Bureau of Standards recently: **Francisco J. Maffei,** director of the Instituto de Pesquisas Tecnológicas of São Paulo; **Luiz C. do Prado,** of the Escola Politecnica of the University of São Paulo; and **Hervasio G. de Carvalho.** Another recent visitor was **Helmuth Stark,** professor at the Technical University of Berlin and a member of the German Standards Institute.

The Académie des sciences, Institut de France, has announced that **Louis Malleret,** director of l'Ecole française d'extreme orient, Hanoi, has been designated Pacific Science Council member from Viet Nam. He succeeds **Maurice Bayen,** who recently resigned on leaving Viet Nam to return to France.

Kenneth D. Nichols, deputy director of guided missiles within the Office of the Secretary of Defense, has been named Army service member of the Department of Defense Research and Development Board. General Nichols succeeds **Ward H. Maris,** who will serve as his deputy. General Nichols is chief of research and development, Office of the Army Chief of Staff. General Maris is deputy assistant chief of staff, G-4, for Research and Development. **Rex Beasley,** who has been serving as deputy to General Maris on the Research and Development Board, will now serve as deputy to **Archibald S. Alexander,** Under Secretary of the Army, who is the Army's civilian member of the Board.

Fred Olsen has been appointed vice president in charge of research and development for Olin Industries, Inc. Dr. Olsen has been with the company since 1929. He is a member of Olin's Board of Directors and most recently has been its director of research and development.

Robert K. Phelan and **Russell C. Roberts,** long associated with the Beech-Nut Packing Company, have formed a company that has purchased the business of Dow B. Hover, Germantown, N. Y., breeder of mice for laboratory research purposes. Mr. Phelan, a member of the Beech-Nut laboratory staff, has been associated with Mr. Roberts in breeding laboratory mice for several years, in an organization known as the Research Animal Farms, Canajoharie, N. Y.

Harold J. Plumley, formerly deputy chief of the Engineering Department at the Naval Ordnance Laboratory, has become chief of the Physics Research Department. **Leslie W. Ball,** who was head of the latter department, was transferred to NOTS, Pasadena, as associate head, Underwater Ordnance Department.

William B. Youmans has been appointed chairman of the Department of Physiology in the University

of Wisconsin Medical School. Dr. Youmans held a similar post at the University of Oregon. The university is to lose the services of **J. A. E. Eyster**, present department chairman, and **Walter J. Meek**, through retirement. The regents also approved appointment of 11 members of the Madison Veterans Administration Hospital as assistant clinical professors.

Education

A **Brazilian Cancer Research Center** will be established in honor of Napoleão Laureano in João Pessoa, his birthplace. One of Brazil's best-known cancer specialists, Dr. Laureano himself died of cancer last May at the age of 36. It is hoped that the hospital may be opened by next January.

MIT will offer a special program in food technology June 16–July 3. The course, which will be under the direction of Bernard E. Proctor, is planned for those in the food industry who may wish to study recent developments and for advanced engineering and chemistry students.

Four new science buildings—biology, chemistry, physics, and geology—are under construction at the **University of New Mexico.** The latest to be started is the $900,000 geology building, which will include a museum, laboratories, and quarters for four branches of the U. S. Geological Survey—Fuels, Ground Water, Quality of Water, and Surface Water—and for the regional office of the Cartographic Division of the U. S. Soil Conservation Service.

The **University of Pennsylvania Museum** has established a radioactivity laboratory for the carbon 14 dating of Middle Eastern archaeological findings, including Hotu man, whose remains were discovered by a Museum expedition in northern Iran last year. When these studies, which are expected to last several months, are completed, the method will be employed to test arctic relics brought back from Alaska in 1950. Carbon 14 laboratories that have been established at Columbia, Yale, and the universities of Chicago and Michigan have chosen other fields of study.

The **Philadelphia College of Pharmacy and Science** and the **Jefferson Medical College** and **Hospital of Philadelphia** will offer a program of graduate study and internship in hospital pharmacy to a limited number of recent graduates of accredited schools of pharmacy. Combined instruction and internship in the three institutions will be for a period of approximately 22 months. Further information may be obtained from Louis A. Reber, of the College of Pharmacy and Science. Applications must be returned not later than *Apr. 1.*

Virginia Polytechnic Institute will conduct a special summer session in its Department of Statistics and its Statistical Laboratory in cooperation with the Departments of Mathematics and Industrial Engineering, July 29–Aug. 15. Graduate students, research workers, and technicians in government and industry may study the statistics of taste testing, bioassay, sampling, and engineering research and production.

Grants and Fellowships

Armour and Company has established a graduate scholarship in food engineering at Illinois Institute of Technology for the academic year 1952–53 and, in addition, has made funds available for special food engineering equipment.

New York University Graduate Program of Studies in the United Nations and World Affairs offers graduate assistantships paying $1250 for 10 months. Application should be made before *May 1* to the director of the program, New York University, Washington Square, New York 3.

Sharp & Dohme has awarded $3600 to Arthur C. Cope, of the Department of Chemistry, MIT, for applied research in new chemical fields, and $1500 to Robert Graham, of the College of Veterinary Medicine, University of Illinois, for studies on the value of sulfonamides and antibiotics in the treatment of diseases of domestic animals and poultry.

Teaching fellowships for 10 months beginning Sept. 1 are available in the Division of Chemistry, **University of Tennessee** School of Biological Sciences. Further information may be obtained from T. P. Nash, Jr., 874 Union Ave., Memphis 3.

United Cerebral Palsey has made a grant of $12,500 to the Physical Therapy School of Northwestern University, to enable the school to continue its training of therapists for another year. The school had been about to close for lack of funds.

Meetings and Conferences

The **American Association of Colleges of Pharmacy** will hold a seminar for teachers of pharmaceutical chemistry at the University of Michigan July 7–12. Tom A. Rowe, dean of the university's College of Pharmacy, will be chairman of the seminar committee.

Sydney Ferguson, board chairman of the Mead Corporation, was elected president of the **American Paper and Pulp Association** at its annual meeting in New York in February. He succeeds George Olmsted, Jr., president of the S. D. Warren Company.

A Conference on the Common Cold was held by the **Common Cold Foundation** in Chicago in February. Thomas G. Ward, of Johns Hopkins, was guest speaker, and his talk was followed by a panel discussion. William A. Sawyer, medical consultant of Eastman Kodak Company, is president of the foundation.

The **Federation of American Societies for Experimental Biology** will hold a joint meeting of scientific groups representing the basic medical sciences in New York Apr. 14–18 at the Statler, New Yorker, McAlpin, and Governor Clinton hotels.

Miscellaneous

The **Air Force Special Weapons Command** at Kirtland AFB, Albuquerque, will be made a part of the Air Research and Development Command, Baltimore, about Apr. 1, to operate under the name of Air Force Special Weapons Center. This integration will facilitate USAF participation in research and development in atomic energy.

Volume 1 of an *Annual Review of Nuclear Science* will be published by Annual Reviews, Inc., in April, under an agreement with the National Research Council. Volume 1 was under the editorial supervision of the NRC Committee on Nuclear Science, and contains 26 reviews. The volumes will be similar to the seven annual reviews now being published, and future volumes will appear under the direction of James G. Beckerley as editor, Donald F. Mastick, Martin D. Kamen, and Leonard I. Schiff as associate editors, and an Editorial Committee consisting initially of C. D. Coryell, L. F. Curtiss, E. Segre, R. E. Zirkle, and Dr. Schiff.

The **Norwegian-Swedish-British Antarctic Expedition,** which has been working for more than two years around Queen Maude's Land and other remote south polar regions, has returned with a great deal of glaciological, geological, and meteorological data. The expedition consisted of 15 members, in addition to a group of Swedish aviators who joined the research vessel *Norsel* at Maudheim, its permanent base. Large areas were mapped from an altitude of 13,000 feet, especially along the eastern shore of the Weddell Sea. Primitive animal and vegetable life—lichens, mosslike organisms, and acarines—were discovered on exposed rock surfaces. These were transported to Europe for study.

The eleventh **Science Talent Search** ended Mar. 3, with a banquet in the Hotel Statler, Washington, D. C. Karl H. Muench, 17, of Evanston, Ill., won the $2800 Grand Science Scholarship, and Robert T. Braden, 18, of Princeton, N. J., placed second. Mr. Muench plans to study medicine at Harvard, and Mr. Braden hopes to enter Cornell to study mathematical physics or electrical engineering. An additional $6200 in scholarship funds was presented to the remaining 38 boys and girls who were the finalists in the annual nation-wide talent hunt, which is conducted by the Science Clubs of America through Science Service, and supported by the Westinghouse Educational Foundation.

Recent Deaths

Clifford Arnold (63), physical medicine rehabilitation specialist, Tucson, Ariz., Jan. 26; **Harry D. Batchelor** (71), chemist, Cleveland, Jan. 22; **Arthur E. Bendelari** (72), of Cincinnati, mining engineer, Lexington, Ky., Feb. 10; **Francis G. Blake** (64), epidemiologist, Washington, D. C., Feb. 1; **Barnabas Bryan, Jr.** (70), geologist and mining engineer, New York, Feb. 5; **William S. Calcott** (59), research chemist, Philadelphia, Feb. 15; **Joseph L. Cartledge** (57), of Morgantown, W. Va., geneticist, New York, Jan. 26; **George H. Chase** (77), educator, Cambridge, Mass., Feb. 2; **Francis D. Coman** (56), Arctic physiologist, Fort Churchill, Manitoba, Jan. 28; **Agnes M. Conklin** (58), psychiatric social worker, Brooklyn, Feb. 3; **Jefferson D. Crane** (43), civil engineer, Miami, Jan. 20; **Chester W. Crumrine** (62), electrical engineer, Rochester, N. Y., Feb. 6; **Patrick E. Gear** (—), surgeon and urologist, Holyoke, Mass., Jan. 20; **Bernard N. Gottlieb** (52), ear, nose, and throat specialist, New York, Jan. 30; **Herbert E. Gregory** (82), geologist, Honolulu, Jan. 23.

Henry H. Haft (60), internist, Syracuse, N. Y., Jan. 23; **Hugh D. Haley** (51), inventor and mechanical engineer, Drexel Hill, Pa., Feb. 8; **Philip W. Hall** (75), inventor, New Brunswick, N. J., Feb. 17; **Fred H. Heath** (69), chemist, Gainesville, Fla., Jan. 26; **Leicester B. Holland** (69), archaeologist, Philadelphia, Feb. 7; **Edward C. Homer** (58), electronics engineer, Water Mill, N. Y., Jan. 28; **Edgar E. Hume** (62), surgeon, Washington, D. C., Jan. 24; **Clinton E. Hurlock** (71), mechanical engineer, Cleveland, Jan. 20; **David S. D. Jessup** (82), of New York, pathologist, Detroit, Feb. 2; **Harry J. Kelly** (68), civil engineer, Pittsburgh, Jan. 20; **Morris E. Leeds** (82), founder and chairman of the board, Leeds & Northrup C·., Lake Wales, Fla., Feb. 8; **Jennings S. Lincoln** (59), physician, Upper Montclair, N. J., Jan. 21; **James L. Mangano** (64), physician, Rochester, N. Y., Feb. 2; **Nelson F. Mellin** (42), chemist, Glen Rock, N. J., Jan. 17; **Ralph D. Mershon** (82), electrical engineer, Miami, Feb. 14; **William H. Nicholas** (53), assistant editor, *National Geographic Magazine,* Washington, D. C., Feb. 7; **Francis E. O'Brien** (56), tuberculosis specialist, Northampton, Mass., Feb. 15; **Frank O'Leary** (61), gynecologist, Toronto, Feb. 3.

Benjamin A. Parry (67), meteorologist, Passaic, N. J., Feb. 12; **Francis W. Pennell** (65), botanist, Media, Pa., Feb. 3; **Liss C. Peterson** (53), acoustical engineer, Chatham, N. J., Jan. 28; **Marius Reboul** (79), chemist, Geneva, Switzerland, Jan. 24; **Jules Redish** (41), heart specialist, Lynbrook, N. Y., Jan. 18; **Louis F. Rodewig** (51), electrical engineer, New York, Feb. 7; **John A. Roebling** (84), engineer, Bernardsville, N. J., Feb. 2; **Charles Scribner** (62), book publisher, New York, Feb. 11; **Harold W. Smith** (74), surgeon, Bethesda, Md., Feb. 4; **S. Dale Spotts** (56), surgeon, Philadelphia, Feb. 1; **Samuel N. Spring** (77), forester, Atlanta, Feb. 3; **Reginald E. Stradling** (60), civil engineer, Shrivenham, Eng., Jan. 26; **Walter T. Swingle** (81), botanist, Washington, D. C., Jan. 19; **Wilbur R. Tweedy** (61), biological chemist, Hines, Ill., Nov. 23; **Edward B. Vedder** (73), pathologist, Washington, D. C., Jan. 30; **Ernest L. Walker** (81), bacteriologist, Atherton, Calif., Jan. 19; **Donald F. Warner** (56), engineer, Marblehead, Mass., Feb. 12; **Carroll H. Wegemann** (72), geologist, Denver, Colo., Jan. 5; **John J. Wolford** (48), of Oxford, Ohio, geologist, Dayton, Feb. 19.

Technical Papers

Charge Distribution in Nuclei from X-Ray Fine Structure[1]

A. L. Schawlow[2] and C. H. Townes[3]
Department of Physics, Columbia University, New York

Since an atomic nucleus occupies a finite volume, electrons are less tightly bound than they would be to a point nucleus with the same charge. The amount of this reduction is greatest for an s electron, which has a large probability of being near the nucleus, less for a $p_{1/2}$ electron, and much less for a $p_{3/2}$ or d electron. This effect has previously been detected only as small differences in the electronic spectra of two or more isotopes, produced by small differences in the size of the isotopic nuclei. Experimental observations of this "isotope-effect" splitting are usually less than theoretical predictions by about a factor of two.

The entire shift rather than isotopic variations due to the finite nuclear volume may be determined from x-ray spectra. Thus it should appear in the separation of the L II and L III x-ray energy levels, which is the difference in binding energy of a $2p_{1/2}$ and a $2p_{3/2}$ electron. Conversely, if the separation is calculated allowing for interaction with other electrons (*1*), a discrepancy remains which can be used as a measure of the nuclear size.

The expected order of magnitude of the nuclear effect can be calculated by the method of Broch (*2*) using the normalization method for p electrons of Rosenthal and Breit (*3*). With the nucleus assumed to be, as indicated by nuclear scattering experiments and radioactivity, a sphere of radius $1\cdot5\times10^{-13}A^{1/3}$ cm, where A is the atomic mass, the fractional change in x-ray fine structure has been calculated. Since the distribution of charge in the nucleus is not known, the calculation has been made for the two extreme cases of a uniform charge density in the nucleus and a concentration of all nuclear charges on the surface. The effect increases very rapidly with Z, being as large as about 1/300 of the fine structure splitting for $Z=90$. The calculated fractional change in the L II–L III separation may be represented very nearly by $f=C(e^{bZ}-1)$, where $b=.0831$ and $C=7\cdot32\times10^{-7}$ for the uniform charge density and $11\cdot2\times10^{-7}$ for the charge on the surface of the nucleus. Since the nuclear size correction varies so rapidly with Z, it may be distinguished from atomic effects, even when the exact magnitudes of some of these atomic effects are unknown.

Christy and Keller (*1*) have used the observed x-ray fine structure splittings to calculate the fine structure constant. In their calculation, screening of the L shell electrons by each other and by the K electrons was taken into account, but nuclear size was not considered. When their final value of $1/\alpha$ is corrected approximately for quantum electrodynamical interactions by using the anomalous g value of the electron (*4*), one obtains $1/\alpha=137.11$. This is .05% higher than the value 137.043 given by other accurate measurements (*5*). When the nuclear size effect is included, assuming uniform charge distribution in the nucleus, the x-ray value of $1/\alpha$ is reduced to 137.04 in good agreement with other values.

When the effects discussed by Christy and Keller (*1*) and nuclear size are both taken into account the fine structure splitting is given by

$$\frac{\Delta\nu}{R}=\phi+BZ^2+C\,\frac{\Delta\nu}{R}\left(e^{bZ}-1\right),$$

where $\frac{\Delta\nu}{R}$ is the fine structure splitting in Rydbergs, and

$$\phi=\frac{2}{\alpha^2}S(\alpha Z)-2\alpha^2Z^2f(\alpha Z).$$

The first term of ϕ is the Sommerfeld expression for the fine structure, and the second term is a correction calculated by Christy and Keller (*1*). B and C are constants which were determined by making a least square fit of the observed fine structure splittings[4] for $Z=70$ to 92, with weights proportional to $1/Z^2$ and using $\frac{1}{\alpha}=137.043$. In this manner we obtain $B=4\cdot816\times10^{-4}$ and $C=-9\cdot55\times10^{-7}$. As a test of the sensitivity of the fit to C this parameter was varied and B re-evaluated by least squares. A 50% change in C in either direction doubles the error squared sum, so that a probable error of about 25% is to be expected.

Thus C deduced from the experimental values is somewhat larger than that for uniform charge density but only by the amount of the experimental error. If nuclear polarization effects are significant, they should decrease the observed value of C. It may hence be concluded that charge is either uniformly distributed in the heavier nuclei or slightly denser toward the surface. Perhaps precise x-ray measurements of some of the heavier elements could improve the accuracy with which this electron-nuclear interaction is known.

The related effect of isotope shift in optical spectra of heavy elements has a magnitude smaller by a factor of two than that calculated using a radius $r=1.5\times10^{-13}A^{1/3}$ and uniform charge density (*6*). The present results exclude the possibility that the charge is concentrated enough toward the center of the nucleus to account for the discrepancy.

[1] Work supported by the Atomic Energy Commission.
[2] Now at Bell Telephone Laboratories, Murray Hill, N. J.
[3] We wish to thank J. W. M. Du Mond for valuable advice and help in evaluating the x-ray data, N. Kroll and G. Series for discussions, and E. Wasilewski and J. Lotspeich for the considerable amount of computing involved in this work.

[4] Obtained from the tabulation of $\lambda L\beta_1$, and $\lambda L\alpha_2$, in Y. Cauchois and H. Hulubei, *Longueurs d'Orde des Emissions X et des Discontinuities d'Absorption X*. Paris: Hermann et Cie (1947). (One of the values for Pb is misquoted in this table.)

An alternative explanation for the smallness of the isotope shifts is obtained if one realizes that the last added neutrons should be approximately uniformly distributed over a region including a dense core of nuclear matter and a less dense region at the nuclear surface about 1.5×10^{-13} cm thick. Then only the part of the neutron wave function inside the core radius is effective in displacing protons outward and so causing isotope shifts. The isotope shift is hence about 50% of that calculated when the gradual decrease in nuclear density at the surface is neglected.

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Manuscript received November 19, 1951.

An Artificial Kidney—A Simplified Apparatus

John R. Guarino and Louis J. Guarino

Brusch Medical Center, Cambridge, Massachusetts and Pan-Engineering Company, New York

The object of this report is to present and to describe an apparatus suitable for routine clinical use as an artificial kidney. It is of small size, is simple in design and construction, and has uncomplicated and safe operation.

The ideal indications for use of an artificial kidney may be found in acute reversible conditions causing retention or a critical increase of the crystalloid metabolins, or of other diffusible toxic products in the blood. It becomes necessary then to remove the toxic products by artificial means to sustain life for the period of repair. Such conditions may be mechanical or pathologic, of renal, extrarenal, or mixed origin. They include the nephritides of acute toxemias, of infection, pregnancy, and poisons; the nephroses such as the bichloride of mercury kidney; trauma to kidneys and ureters causing anuria; urinary obstructions; anuria following blood transfusions, severe burns; poisoning caused by diffusible chemicals, such as the barbiturates, sulfonamides; crystalloid and electrolyte imbalance.

The extrarenal routes attempted for excretion of retention products include skin, peritoneal lavage, gastrointestinal tract, kidney transplantation, crossed blood transfusion, plasmapheresis, perfusion through an isolated loop of intestine, and vividialysis or vividiffusion (artificial kidney).

The artificial kidney, a method of vividialysis, has proved the most effective and practical means for the extrarenal excretion of retention products. This work began with Abel, Rowntree, and Turner, in 1913 (*1*), and was followed by Haas (*2*) and Thalhimer (*3*). With the use of heparin in place of the more toxic hirudin, and cellophane as the dialyzer in place of collodion, celluidin, or peritoneal membrane, further progress continued with Kolff (*4*), Murray, Delorme, and Thomas (*5*), Lam and Ponka (*6*), Alwall (*7*), Skeggs and Leonard (*8*), Vanatta, Muirhead, and Grollman (*9*), and Merrill, Smith, Callahan, Thorn, and Walter (*10*).

The various apparatus differ in design, but are basically similar and have one common principle: blood of the subject is introduced through a cellophane tube which is immersed in a bath of perfusion fluid. The diameter of the tube ranges from 0.1 cm to 2.54 cm, with lengths of 10–45 m. The tubing is arranged in parallel series, wound spirally about a vertical stationary drum, or spirally about a horizontal revolving drum. The volume of the bath fluid has varied from 25 to 100 liters, and the fluid is stationary, or it is agitated by a motor-driven propeller. A blood volume of 0.5–1.0 liter is contained in the tubing. To reduce the blood volume and the size of the apparatus, Alwall (*7*) maintains compression of the cellophane tubing by a special device; Skeggs (*8*) employs a series of "kidney units," each consisting of a single layer of sheet cellophane between two corrugated rubber pads.

These systems are necessarily large or complicated and present serious operational and technical difficulties. In circulating a large volume of blood through such extensive extracorporal systems, blood clotting, sterility, hemolysis, pyrogen reactions, blood flow, blood viscosity, hemorrhage into the tubing, and requirements of large amounts of heparin become major problems and increase the operational risk, limiting the use of the artificial kidney as a routine clinical procedure. Although the therapeutic value of the artificial kidney is well established, the treatment is considered radical and heroic.

Our apparatus is shown in Fig. 1. It consists of a silicone-coated glass chamber, with a detachable upper portion. There are conduits attached for the entrance and exit of blood, and for the entrance and exit of a prepared rinsing or perfusion fluid. Twenty-three ft of ¾-in. cellophane tubing are incorporated in the chamber in concentric layers. The cellophane tubing requires no support and is simply placed in the chamber with its free ends connected to a reservoir containing the rinsing fluid. A continuous circulation of the rinsing fluid is first established through the cellophane tubing in the chamber. The fluid leaves the reservoir through conduit "*A*", and is pumped through conduit "*B*" into the cellophane tubing in the chamber, and leaves the chamber through conduit "*C*" to return to the reservoir, providing a continuous flow of the rinsing fluid through the cellophane tubing. This circulation of the fluid can be accomplished by gravity; however, since this would require two reservoirs and manual attention, it has been found preferable to use

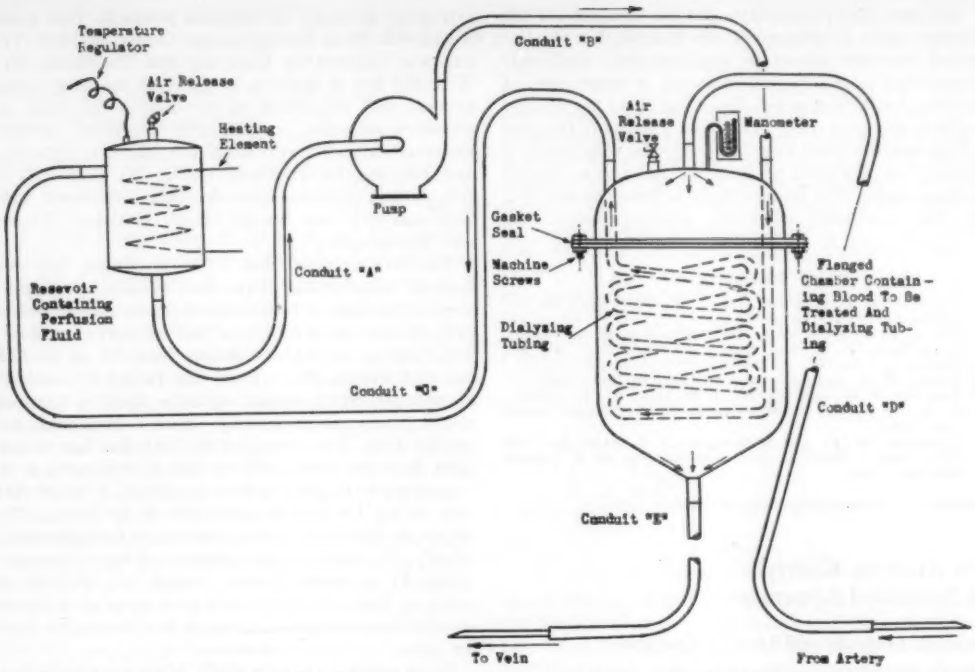

FIG. 1. Schematic diagram of artificial kidney. Diameter of chamber, 4"; length of chamber 7"; length of dialyzing tubing, 23'; diameter of dialyzing tubing, ¾"; dialyzing surface area, 4115 sq cm; volume of blood in chamber, 50 ml.

a pump to circulate the rinsing fluid. Circulation through the cellophane tubing, arranged as described, is controllable and has been maintained without difficulty at rates up to 300 ml/min. A mixture of oxygen and carbon dioxide may enter the reservoir to control the pH of the fluid.

The radial artery of a subject is exposed and interrupted, and a cannula is inserted into the proximal stump. Blood will flow from the subject through conduit *"D"* into the chamber, and leave the chamber through conduit *"E"* to return to the subject. As the blood enters the chamber, an air cushion is formed above the surface of the blood. The air cushion and air vent may be used to control the volume or level of blood in the chamber (*11*). The hydrostatic pressure of the perfusion or rinsing fluid is maintained equal to, or above, the hydrostatic pressure of the blood. The blood is allowed to flow over the cellophane tubing in a nondirectional flow, forming, in effect, a blood shower. The treated blood leaves the chamber through conduit *"E"* and is returned to the subject through a cannula inserted into the distal stump of the radial artery or to a suitable vein. An artery-to-artery flow in place of artery-to-vein may eliminate the adverse effect of an arteriovenous shunt that is present in the latter method at high flow rates. Fig. 2 shows a convenient method by which an artery-to-artery flow is accomplished with the use of a double-passage cannula. The cannula is of sufficient length to extend outside the operative field. It avoids clutter at the site of dissection and requires only one cut-down.

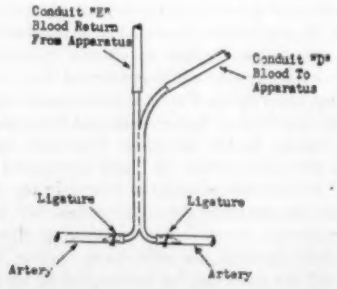

FIG. 2. Schematic diagram of artery-to-apparatus-to-artery blood flow with use of single double-passage cannula.

In the one chamber, then, there is formed at the same time, in a closed system, a continuous circulation of blood enveloping a continuous cross-circulation of the perfusion fluid. The dialyzing tubing with its circulating rinsing fluid may occupy part or nearly the whole volume of the chamber. Since the volume of the blood in the chamber is controlled, a very large dialyzing surface area can be exposed, utilizing only a minimum amount of blood, eliminating dead space and excess or waste blood. The efficiency of the ap-

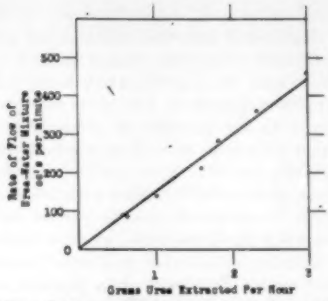

FIG. 3. The effect on rate of urea extraction with increasing flow rate of urea-water mixture. Dialyzing surface area, 1370 sq cm; rate of flow of perfusion fluid, 100 cc/min; urea nitrogen in urea-water mixture, 226 mg%; temperature of urea-water mixture and perfusion fluid, 65° F; volume of urea-water mixture in chamber, 50 cc; volume of perfusion fluid in reservoir, 4 liters; length of cellophane tubing, 7½'.

paratus is greatly increased thereby and permits a small-sized chamber.

There is a rapid change of blood in cross-circulation with a rapidly changing rinsing fluid. In this way the concentration of the diffusible substances in the blood will be constantly maximal, and the concentration of the diffusate in the perfusion fluid can be maintained near zero. This allows highest diffusion gradients to exist at all times between the blood and the perfusion fluid. These conditions are conducive to a maximal rate of diffusion.

In a tubular blood flow of other systems, dialysis occurs only with the layer of blood at the periphery of the tube in contact with the dialyzing membrane; the blood away from the periphery is surplus. Furthermore, the blood flow at the periphery of the tube is slowest, and this factor becomes increasingly important as the viscosity of the blood increases, and when the rate of blood flow decreases.

Since the amount of the blood used in this apparatus is small (10–50 ml), and since the blood traverses a very short extracorporal path, the heart of the subject functions very efficiently as the sole propagating force. This has been demonstrated with the application of the apparatus on dogs, where a pulsating blood flow can be maintained with negligible loss of blood pressure gradients.

The efficiency and capacity of the apparatus have been studied, using urea-water mixtures and water. The actual experimental values are plotted in graphs (Figs. 3, 4). Similar results were obtained with human blood. In consideration of possible errors in measuring flow rates and in computing the actual dialyzing surface area, since the tubing was never fully inflated, an average trace was made in each case.

In Fig. 3 a straight-line relationship is evident between the rate of flow of urea-water mixture and amount of urea extracted, with the dialyzing surface area and rate of flow of perfusion fluid remaining constant. As the rate of flow of urea-water increases, the amount of urea extracted increases directly.

In Fig. 4 a straight-line relationship is also evident between the dialyzing surface area and the amount of urea extracted, with the rate of flow of urea-water and the rate of flow of perfusion fluid remaining constant. As the dialyzing surface area increases, the amount of urea extracted increases directly.

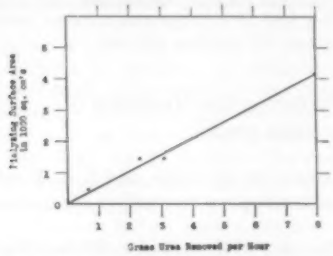

FIG. 4. The effect on rate of urea extraction with increasing dialyzing surface area. Rate of flow of urea-water mixture, 240 ml/min; urea nitrogen level, 213 mg%; rate of flow of perfusion fluid, 75 cc/min; volume of urea-water mixture in chamber, 50 ml; volume of perfusion fluid in reservoir, 4 liters; temperature of urea-water mixture and perfusion fluid, 65° F.

In the apparatus, which is 4 in. in diameter and 7 in. long, and which contains 23 ft of tubing with a dialyzing surface area of approximately 4115 sq cm, 8 g urea/hr were removed. The rate of flow of the rinsing fluid through the tubing was approximately 75 ml/min, and the rate of flow of urea-water mixture was 240 ml/min.

This apparatus in its present capacity is a highly efficient artificial kidney. The chief advantages are:

1) Small size of apparatus, with simplicity of construction and operation;

2) Requirement of small amount of blood in the chamber for a large dialyzing surface area;

3) Elimination of blood pumps, machinery, and air traps;

4) A rapid change of blood in a nondirectional flow;

5) A constant change and circulation of perfusion fluid, with no evaporation of fluid;

6) No opportunity for reabsorption of the diffusate by the blood;

7) The requirement of a minimum amount of cellophane tubing and perfusion fluid;

8) The need for only a small amount of heparin;

9) Elimination of problems of blood circulation, blood clotting, hemorrhage, blood viscosity, sterility, hemolysis, pyrogen reactions, and heparin toxicity.

This artificial kidney is small, safe, and efficient, and can be used with little difficulty in small hospitals and clinics as a routine treatment.

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Manuscript received November 14, 1951.

Blood Factors in the Nutrition of *Trypanosoma cruzi*[1]

W. L. McRary, E. R. Noble, and E. L. Tondevold
Santa Barbara College of the University of California

Although successful media for the *in vitro* culture of the blood parasite *Trypanosoma cruzi* invariably contain blood or blood derivatives, the nature of the essential blood factors remains ill defined. It appears likely from the work of numerous investigators that hemoglobin is one source of these factors (reviewed by M. Lwoff [*1*] and von Brand [*2*]). Little and his associates (*3–5*) have described media containing as their sole blood component a coagulum made from rabbit erythrocytes, or chick red cells applied on filter paper and autoclaved. Other writers (*6*) have stated that hemoglobin is not necessary. We have obtained satisfactory results using human red cell coagulum in conjunction with a basal medium of glucose, NaCl, and peptone in the concentrations recommended by Little and SubbaRow (*3*). Attempts to extract, concentrate, and identify the essential nutrient or nutrients from the solid coagulum have not been successful. The following experiments, however, have led us to the conclusion that the active principle for our strain of the parasite is a derivative of hemoglobin.

Thrice recrystallized hemoglobin was prepared from 6 times washed human erythrocytes by the method of Drabkin (*7*). The protein was then dissolved in water, dialyzed until essentially free of salts, and stored under sterile conditions after Seitz filtration. Cultures were carried out in a diphasic medium consisting of a 3-ml agar slant and a 2-ml liquid overlay. The basal medium containing 0.2% glucose, 0.5% NaCl, and 2% peptone at pH 7.4 was used in both the agar and liquid phase. Three to 4 mg of hemoglobin was added to the agar phase prior to autoclaving, the agar being used primarily as a solidifying agent. Each subculture was carried out in sextuplicate, using 0.1 ml inocula from the preceding culture, serial transfers being made at 18–22-day intervals, at which time the parasite count was about 12,000,000/ml.

Starting from a stock culture originally obtained from Costa Rica through the courtesy of Herbert Johnstone, of the University of California Medical Center, and grown by us on human red cell coagulum, agar, glucose, NaCl, and peptone, we have carried the organism through 13 serial transfers on the hemoglobin medium, with no diminution in rate of reproduction. Concurrent with the eighth serial subculture, a series of media containing graded amounts of hemoglobin from none to approximately 3 mg was inoculated. Growth responses in this series were essentially proportional to the amount of hemoglobin present. Substitution of hemin, of acid or peptic hydrolysates of hemoglobin, and of a heme-globin mixture for the heat-treated protein have yielded negative results. We were unable to maintain growth beyond the second subculture when the hemoglobin was not heated; however, the addition of ascorbic acid or of serum to unheated hemoglobin has resulted in positive responses to date through 5 and 8 subcultures, respectively.

On the basis of these observations it appears that a moderately complex derivative of hemoglobin is the only additional essential growth factor for our strain of *T. cruzi* when peptone, glucose, and NaCl are present in the medium. Work is in progress in an attempt to determine the nature of the active substances arising from the heat treatment of protein. As part of this investigation other heme-protein combinations are also being studied.

[1] These studies were aided by a contract between the Office of Naval Research, Department of the Navy, and the University of California.

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Manuscript received August 20, 1951.

The Archaeological and Paleontological Salvage Program at the Medicine Creek Reservoir, Frontier County, Nebraska

E. Mott Davis and C. Bertrand Schultz
Divisions of Anthropology and Vertebrate Paleontology, University of Nebraska State Museum, Lincoln

This report summarizes the results of scientific salvage operations during the past six years by the University of Nebraska State Museum at the Medicine Creek Reservoir. Medicine Creek is a major northern tributary of the Republican River in the dissected loess plains of southwestern Nebraska.

The Bureau of Reclamation completed work on the Medicine Creek Dam in 1949 as part of the Missouri Basin Development Program. Several archaeological and paleontological sites were destroyed in the course of construction work, and many more have been inundated by the Medicine Creek Reservoir, which reached normal pool level in 1951. Following the pattern set for reservoir projects throughout the Missouri Basin, a number of institutions participated in a salvage program aimed at the recovery of as much information as possible from these sites before they were destroyed.[1]

[1] There had been field work in the Medicine Creek Valley previous to the salvage investigations described here (*1–3*).

The Missouri River Basin Survey of the Smithsonian Institution and the Nebraska State Historical Society conducted archaeological work, which has been reported elsewhere (*4*). The University of Nebraska State Museum undertook paleontological and geomorphological investigations, which later were accompanied by archaeological work.

Seven major localities have been intensively investigated by Museum parties.[2] Three of these sites are of late Pleistocene age, and four are late Pliocene.

The late Pleistocene localities proved to be of more than purely paleontological interest, since the faunal material in them was associated with evidences of human activity. These three sites are the Lime Creek Site (Ft-41), the Red Smoke Site (Ft-42), and the Allen Site (Ft-50).[3] All are in the lower part of the fill of Republican River Terrace-2A, tentatively dated as Mankato (Wisconsin-IV) (*5, 6*). The sites originally appeared as strata containing bone fragments, flint, and charcoal in the faces of vertical loess cliffs along Medicine Creek and its tributary Lime Creek. Excavation has revealed bowl-shaped fireplaces without stone lining, burned and broken bones, piles of flint chips, and occasional stone and bone artifacts, among which the most significant diagnostic items are projectile points. No human skeletal material, except for a single phalanx, has been recovered.

At the Lime Creek Site an upper stratum contained two points almost identical with certain of those illustrated by Krieger from the Plainview Site in Texas (*7*). Separated from this stratum by 8 ft of undisturbed silts was a lower occupation level, which has been reported previously (*8*). Parallel-sided points with straight bases came from this level. Charcoal obtained from 1 to 2 ft below the lower occupation level, but in the same sedimentary unit, has been given a radiocarbon date of 9524 ± 450 years (*9*).

The Red Smoke Site contains at least eight strata with artifacts and other evidences of human activity. From a middle layer has come a series of points and point fragments that correspond in form to Krieger's Plainview type (*10*). The other occupation levels have not yielded diagnostic material.

The Allen Site has been reported by Holder and Wike (*11*). They find that the artifact complex, which differs from those mentioned above, resembles most closely that found at Deadman Cave in Utah (*12*). Radiocarbon dates from the Allen Site are not consistent (*13*), but dates of 8274 ± 500 and 10,493 ± 1500 years for charcoal from the lower part of the occupation zone are felt by the present authors to be the most reliable ones in terms of the total evidence.

[2] This work was supported in part by funds from the following: Hector Maiben, Mr. and Mrs. Ben Maiben, and Childs Frick funds through the University of Nebraska Foundation; the University of Nebraska Research Council; the National Park Service; and the U. S. Bureau of Reclamation. The cooperation of the Missouri River Basin Survey of the Smithsonian Institution is also acknowledged.

[3] The code site designations used here are those employed by the Museum. According to the site designation system used by the Smithsonian Institution and several other organizations, these sites would be listed as 25FT41, 25FT42, and 25FT50, respectively.

It is impossible, so far, to determine temporal or cultural relationships between the archaeological manifestations found in these several sites, owing largely to the scarcity of diagnostic material. Sedimentary evidence indicates that the strata containing Plainview points at the Red Smoke and Lime Creek sites are approximately contemporaneous, and strengthens the typological conclusion that they are culturally related.

Judging from the evidence in these sites, southwestern Nebraska was occupied in late glacial times by wandering groups of bison hunters. Some of these groups, representing more than one cultural tradition, camped repeatedly along Medicine Creek—probably because of the abundance there of easily worked jasper and the presence of plentiful game. Further work is necessary before it will be possible to determine the local sequence of occupation. This information will then contribute to the broader story of the part played by human beings in the changing ecological situation on the Great Plains during late glacial and early postglacial times.

The paleontological material obtained from the above-mentioned late Pleistocene sites is of special interest because it represents the first extensive fauna from deposits of this age to be reported from the Great Plains region. Some of the faunal elements are similar to modern forms, whereas others appear to represent extinct species. The coyote bones, for example, cannot be differentiated from those of the modern species, *Canis latrans* Say, whereas the samples of bison compare favorably with those of the extinct form *Bison antiquus* Leidy from the late Pleistocene deposits of the Great Plains rather than with the modern *B. bison*. The radiocarbon dates obtained from two of the sites are a valuable aid in the study of the actual rate of evolution that has taken place during the past 10,000 years in a number of phylogenetic lines of mammals. Additional faunal evidence from the more recent terrace fills of the region has provided supplementary data on the rate and trends in evolution. These evolutionary yardsticks may well give us a clearer understanding of mammalian development in the earlier, as well as the later, part of the Pleistocene.

In the late Pliocene localities paleontological work took place primarily in the Kimball formation of the Ogallala group, which contained the remains of the shovel-tusked mastodont *Amebelodon fricki*, as well as various new species of mammals. The most important single specimen salvaged from the Kimball sands was the skull and ramus of a new form of giant saber-toothed cat, not ancestral to the saber-toothed felids of the Pleistocene. The Kimball formation heretofore had yielded only fragmentary faunal evidence in the central Great Plains. The Ash Hollow sediments directly below the Kimball also yielded fossils. The new material has helped to complete the late Pliocene faunal sequence and hence has thrown much new light on the Pliocene-Pleistocene boundary line problem.

An intensive geological and geomorphological study of the Medicine Creek area has accompanied the

archaeological and paleontological work. Detailed reports on all aspects of the Museum's Medicine Creek field project are in preparation.

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Manuscript received October 11, 1951.

Antagonistic Action of Uracil, Thiouracil, and Thiourea on Reticulocyte Ripening

Alphonse Nizet[1]

Institut de Clinique et de Policlinique Médicales, Université de Liège, Belgium

Granulocytopenia and agranulocytosis are well-known complications of the treatment of thyrotoxicosis with the drugs of the thiourea group. A few cases of anemia have been observed (*1–3*). A slight drop in erythrocyte count has been found by Goldsmith, Gordon, Finkelstein, and Charipper (*4*) in rats poisoned by thiourea. According to Weinglass, Williams, Bissel, and Peters (*5*), a decrease of hemoglobin level is evidenced in rats receiving thiouracil. We have previously shown that thiourea, thiouracil, and methylthiouracil inhibit reticulocyte ripening *in vitro* (*6*). Besides, an antagonistic action of thiouracil and uracil on bacterial growth has been observed by Strandskov and Wyss (*7*) and Wolff and Karlin (*8*). On the basis of these observations, it appears quite possible that the inhibiting activity of thiouracil and its derivatives on blood cell ripening and regeneration could be due to an interference with the normal metabolism of uracil. This hypothesis seems to be confirmed, in the particular case of red blood cells, by the experiments described in this paper. The experimental results show a competitive antagonism of uracil, thiourea, and thiouracil on the ripening of young erythrocytes (reticulocytes) *in vitro*.

The observation of reticulocyte ripening *in vitro* has already made possible an experimental investigation of various toxic and metabolic factors concerned with erythropoiesis (*6, 9, 10*). Our technique for the study of reticulocyte ripening has been fully described elsewhere (*9, 11*); it will be summarized here.

[1] Fellow of the Belgian National Fund for Scientific Research.

Blood samples containing 10% heparin-glucose solution (heparin 200 mg %, glucose 1% in NaCl 0.9%) are drawn from adult dogs made anemic by repeated blood withdrawals, the hemoglobin level being maintained around 6–8 g %. The dogs are kept in good health and isolated; worms and other parasites are eliminated. Standard diet includes bread, 250 g; potatoes, 250 g; meat, 150 g; yeast extract, 2 g; and powdered iron, 40 mg daily. The animals submitted to chronic hemorrhage anemia show a high reticulocyte level in the peripheral blood (50–200/1000 RBC) and a normal reticulocyte ripening.

Basal solutions used are prepared as follows:

1)	Thiouracil	200	mg
	NaOH 1/10 *N*	17	ml
	Buffer at pH 7.34 (Na2HPO4 ⅕ *M*-citric acid 1/10 *M*)	3	"
2)	Thiouracil	100	mg
	NaOH 1/10 *N*	7.5	ml
	Buffer at pH 7.34 (Na2HPO4 ⅕ *M*-citric acid 1/10 *M*)	12.5	"
3)	Thiourea, 0.5% and 1% in NaCl 0.9%		
4)	Uracil, 5000, 500, 50, 25, 12.5, 5, 2.5 μg/ml NaCl 0.9%		

The above solutions are added to aliquot portions of the blood samples, in a proportion of 10–20%, in order to obtain concentrations of thiouracil or thiourea of 350–2000 μg/ml blood. The concentrations of uracil in the blood are between 500 and 0.25 μg/ml. Control experiments are performed without thiourea, thiouracil, or uracil supplementation. The blood samples are incubated at 37° C for 6–8 hr. Reticulocyte counts are made at the beginning and at the end of the incubation period, according to our usual technique (*12*) (observation on dark field of *dried* smears after post-vital staining with brilliant cresyl blue), in various parts of each smear, and on a minimum basis of 5000 RBC. Reticulocyte ripening is evidenced by the decrease in reticulocyte number during incubation of the blood. The higher the decrease, the faster the ripening of young erythrocytes. Experimental results are depicted in Tables 1 and 2.

The experiments demonstrate that reticulocyte ripening is slowed or blocked by either thiourea or thiouracil at a range of concentrations between 350 and 2000 μg/ml blood. The block of ripening is evidenced by a reduced decrease of reticulocyte number during incubation of the blood.

The block of ripening is lifted by uracil at considerably lower concentrations (less than 5 μg/ml). After simultaneous supplementation with thiouracil and uracil, or thiourea and uracil, the reticulocyte ripening is normal and proceeds at the same rate as in control experiments. A competitive antagonistic action of thiourea, thiouracil, and uracil on red cell ripening is evidenced.

On the basis of the above-described results it appears very probable that the inhibition of erythropoiesis by thiourea and thiouracil is due to an interference of these drugs with normal uracil metabolism. It should be remembered that uracil is a constituent

TABLE 1

ANTAGONISTIC ACTION OF THIOURACIL AND URACIL ON RETICULOCYTE RIPENING

Experiments		1	2	3	4	5	6	7	8	9	10
Dogs		NLP4	NLP4	L10	NLP4	L10	L10	L10	NLP4	NLP4	NLP4
Incubation time (hr)		6	6	6½	6	6	7	6	7	8	7
No. reticulocytes/1000 RBC before blood incubation		124	77	130	96	131	154	156	75	79	69
After blood incubation	Conc μg/ml										
	Thiouracil	Uracil									
	0	0	78	57	89	62	92	120	105	51	54	43
	350	0	104	71								
	350	500	77	51								
	1000	0			115	87	116	135	149	69	72	
	1000	500				68						
	1000	50			78	72						
	1000	5			81	62	88	102	106			
	1000	2.5						102	108	42	43	
	1000	1.25						111	116		41	
	1000	0.5					99	123	107		49	
	1000	0.25							136	44		
	2000	0										69
	2000	5										44
	2000	0.25										58

TABLE 2

ANTAGONISTIC ACTION OF THIOUREA AND URACIL ON RETICULOCYTE RIPENING

Experiments		1	2	3	4	5	6	7	8	9	10
Dogs		NLP4	L10	L10	L10	B7	NLP4	L10	L10	L10	BB3
Incubation time (hr)		7	7	7	7	7	7	7	7	7½	7
No. reticulocytes/1000 RBC before blood incubation		127	70	127	128	69	92	63	107	151	73
After blood incubation	Conc μg/ml										
	Thiourea	Uracil									
	0	0		50	81	87	44	57	44	76	115	55
	500	0			119	111	60	77	56	96		
	500	5			82	85	40	57	41	77		
	500	2.5			83	88			37	83		
	500	1.25			73					77		
	500	0.5			111	106			40			
	500	0.25			125	104	43	54	51	81		
	1000	0	112	64							147	72
	1000	5	79								116	
	1000	2.5		48								56
	1000	1.25		48							117	
	1000	0.5		48							141	
	1000	0.25	67	60							137	60

of ribonucleic acids concerned with anabolic processes and present in the reticulocytes (*13–15*).

The inhibition of granulocyte regeneration may be caused by the same process. That antithyroid activity might also be the result of a disturbance of uracil metabolism, according to the hypothesis of Poupa (*16*) and Lauter and Stewart (*17*), is possible, but remains to be proved.

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Manuscript received September 17, 1951.

Some New Synthetic Estrogens

H. Rinderknecht[1] and L. W. Rowe

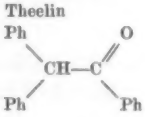
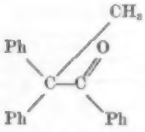
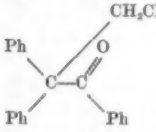
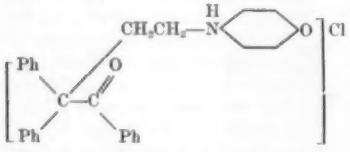
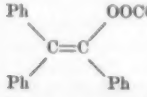
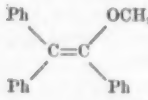
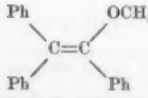
Gates and Crellin Laboratories of Chemistry,[2] California Institute of Technology, Pasadena, and Research Department, Parke Davis & Co., Detroit, Michigan

In the course of an investigation[3] on the alkylation of α: α-diphenylacetophenone (*1*) a series of compounds was obtained which, in view of their structural relationship to triphenylethylene, appeared to be of interest as potential estrogens. Table 1 presents the result of the provisional tests for estrogenic activity. Assays were carried out according to standard procedures.

Although the number of compounds investigated is too small to permit general conclusions as to a relationship between chemical constitution and physiological activity, certain regularities can be observed within a series of homologs. Thus, in the ketone series (1, 2, 3, 4) substitution of the α-position by an aliphatic group increases the activity as compared with the parent substance (1). Maximum activity is shown by the methyl-homolog (2). An increase in the chain length, however, drastically reduces activity (3, 4).

In the second series (5–12) etherification of the enol of α: α-diphenylacetophenone gives, as would be expected, compounds more active than the acetate (5), which presumably is hydrolyzed *in vivo* by esterases. Again estrogenic activity decreases rapidly with increasing chain length of the alkyl group involved in ether formation (6, 7, 9, 10, 12). Although the ethyl ether (6) appears to be the most active nonbasic compound of this group, the methyl-homolog might be expected to exhibit maximum activity, but unfortunately

TABLE 1

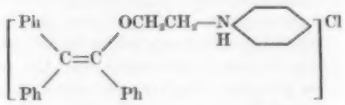
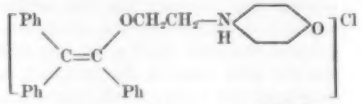
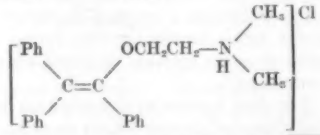
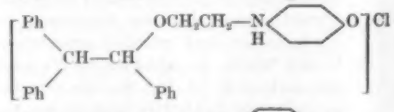
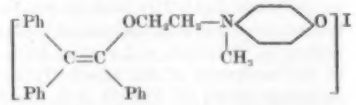
No.	Structural formula	Assayed in	Estrogenic activity in IU/mg
	Theelin		10,000
1.		Aqu. ethanol	10
		Peanut oil	40
2.		Peanut oil	6000
3.		Peanut oil	1000
4.		Aqu. ethanol	< 100
5.		Aqu. ethanol	400
		Peanut oil	400
6.		Peanut oil	5000
7.		Peanut oil	500

[1] Research associate of the Cilag Co., Schaffhausen, Switzerland.

[2] Contribution No. 1600.

[3] The authors wish to express their sincere thanks to G. Rieveschl for his interest and help in this work.

TABLE 1—(*Continued*)

No.	Structural formula	Assayed in	Estrogenic activity in IU/mg
8.		Peanut oil	3000
9.		Peanut oil	100
10.		Peanut oil	200
11.		Aqu. ethanol	< 400
12.		Aqu. ethanol	< 400
		Peanut oil	< 100

it was not available for testing. The only compound that does not fit this general pattern is the β-piperidinoethyl ether (8). No explanation can at present be offered for its surprisingly high estrogenic potency, which is 15 to 30 times that of the analogously constituted compounds (10) and (9). This was confirmed by several reassays.

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Manuscript received October 15, 1951.

Comments and Communications

"Attraction Fields" between Growing Tissue Cultures[1]

Ghosts have a way of refusing to be laid. One such ghost is the alleged "attraction" for each other's cells supposedly exerted by two growing parts—for instance, two tissue fragments cultured in a common medium. More than 20 years ago I gave the first description of the striking phenomenon of an oriented cell bridge forming, under certain conditions, between two growing centers (*1*); for convenience this may be referred to as the "two-center effect." At the same time, and repeatedly since (e.g., [*2*]), I have pointed out that the superficial impression of "attractions" (in the customary sense of the word) being at play is a sheer illusion. The correct interpretation, gained by stepwise analysis of the factors involved, has been amply documented and published (*2–5*). It has found even wider currency through the publications of other authors (*6, 7*).

It is somewhat perplexing, therefore, to find in a recent article in Science (**114**, 431 [1951]) the whole phenomenon rediscovered, redescribed and, by the implications of the terms used, again misinterpreted. In the article in question, entitled "Distance as a Factor in the Development of Attraction Fields between Growing Tissues in Culture," the author, Allan A. Katzberg, states that "the term 'attraction field' has been used to describe this phenomenon." This term is absolutely inappropriate and misleading. Its reaffirmation by the author mars what is otherwise a correct, if not altogether novel, presentation. It matters little that the author is only dimly aware of the systematic work that has been done in this field before. After all, his observations fully confirm the known facts. But the way in which he treats them is apt to lead back to

[1] Work referred to in this paper was aided by the Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago and by a grant-in-aid from the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council.

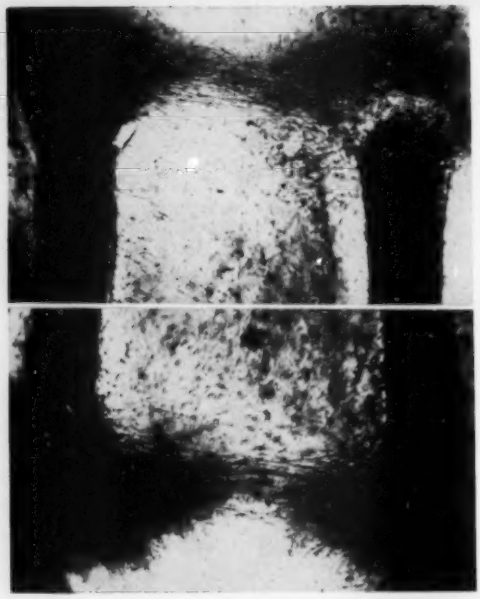

FIG. 1. Two rat nerves, subject to Wallerian degeneration for 17 days, explanted side by side as described in text, fixed after 4½ days *in vitro* and impregnated with silver according to Bodian.

the same old confusion from which our analysis had shown the way out. Therefore, and because of the rather broad implications of the two-center effect for morphogenesis in general, it seems desirable to restate the case briefly.

In order not to be wholly repetitive, I shall use an example not previously published (Fig. 1). Two fragments of adult rat nerve were embedded parallel to each other in a thinly spread clot of fowl blood plasma and embryo extract[2] (thinness of the layer is essential [*2*]). There followed massive outgrowth of sheath cells and fibroblasts from the open nerve ends into the interior of the clot. Near the surface of the clot, however, the cells followed linear, perfectly straight courses reciprocally from one cut end to the other, establishing a cell bridge as striking as in any of our earlier two-center experiments.

As set forth on previous occasions (*1–5, 8, 9*), the mechanism by which this effect is produced has nothing to do with "mutual attraction" but consists of the following sequence of events: (1) The cell masses issuing from the cut ends begin to proliferate, thus constituting local growth centers. (2) Since cell proliferation commonly entails dehydration of the surrounding colloids (*1, 2, 10*), the fibrin around each nerve end undergoes progressive condensation and contraction. (3) These local contractions create tensions in the fibrin net which, for a given amount of proliferation and shrinkage, vary as inverse functions of both volume and thickness of the medium; they are strongest in the surface. (4) For any given medium, the resultant stresses reach a maximum along the connecting line between two foci of contraction. (5) Since the prevailing tensions force the fibrin net into a configuration corresponding to the stress pattern, the fibrin chains, particularly near the surface, are likewise assuming preferential orientation along the connecting line between the two centers. (6) Thus is established a fibrin bridge which acts as a pathway guiding the cells that grow out from either center straight over toward the opposite center. The cells glide over this bridge actively, owing to an affinity for fibrous pathways ("contact guidance"), discussed in greater detail previously (*9*). By no means are they pulled over by traction or lured over by mysterious "attractions."

This, then, is the actual mechanism of the two-center effect. Some of its component steps have, in fact, been correctly recognized by Katzberg; for instance, the condensation and parallel orientation of the fibrin bridge which, in addition to its earlier histological demonstration (*2*, Fig. 8), has now been made visible by polarized light. His main thesis, the decline of the two-center effect with increasing distance between the centers is, of course, self-evident from a consideration of the mechanics of the effect. By consulting an appropriate model (*2*, Fig. 5), it is found that the stress produced by the contraction of the two centers, which is the force aligning the fibrin micellae, is some inverse function of their distance. Just what function, it is difficult to deduce. In an extreme condition, with only a narrow and laterally unattached strip of plasma connecting the two centers, and on the assumption of ideal elasticity of the fibrin net, the linear deformation that is due to a standard degree of contraction e would (according to Hooke's law) be proportional to $\frac{2e}{x}$, where x is the distance. In the actual situation, however, this value will be smaller, because of the continuity of the connecting strip with the rest of the elastic clot, which takes up some of the resulting stresses; further complications arise from the presumable slippage of the stretched fibrin strands, invalidating the applicability of Hooke's law, and the change in mechanical and physicochemical properties of the fibrin chains once they have become aligned and aggregated into larger bundles.

That under these complex conditions the above function should assume the form of exactly an inverse square relation, as reported by Katzberg, seems highly improbable except by coincidence. Moreover, Katzberg's circuitous derivation of this formula from statistical data on the "incidence" of "attraction fields" as a function of distance is rather objectionable, for the two-center effect is basically not an all-or-none condition of "incidence," but a matter of degree. It is true that, as I pointed out in my first report (*1*), the effect has an element of self-reinforcement, so that once initiated it tends to become ever more accentuated as growth proceeds. Even so, there are too many other

[2] This case is taken from a series of experiments done in 1944 with the excellent technical assistance of Hsi Wang.

relevant variables in the picture (e.g., thinness of clot, adhesiveness between clot and cover slip, nearness of culture to surface, meniscus formation, etc.) to put any great stock in a precise quantitative evaluation of the figures of observed "incidence." They do, of course, qualitatively express the general predictable decline of the two-center effect with distance and in this sense are a welcome addition to our knowledge.

These comments should not be construed as discouragement of a more quantitative study of the two-center effect. Indeed, such a study would be highly desirable. But it should be undertaken with a sense of realism—that is, with the nature of the operative mechanism clearly in mind. Perhaps the main danger of a superficial and purely formal treatment is that, if it happens to turn up such empirical data as Katzberg's inverse-square-of-distance relation, and if this is then reported as the property of an "attraction" field, all those unfamiliar with the real situation will jump to the conclusion that this connotes a simple interaction after the fashion of Coulomb attractions. My remarks here are intended to point up the fallacy of such a conclusion. In a wider sense, they may also be taken as a more general plea for greater caution against the rapidly growing indulgence in gross oversimplification in some branches of contemporary biology.

PAUL WEISS

Department of Zoology
University of Chicago

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A FEELING of pleasant surprise was experienced by this writer when he learned that his modest article entitled "Distance as a Factor in the Development of Attraction Fields between Growing Tissues in Culture" (SCIENCE, **114**, 431 [1951]) has attracted the attention of so eminent a scientist as Paul Weiss, upon whom this writer looks as the dean of that field of biology related to growth.

The comments made by Dr. Weiss in the accompanying article are very interesting. However, clarification of some statements is in order. For example, we read: "The author is only dimly aware of the systematic work that has been done in this field." The writer feels certain that Dr. Weiss does not sincerely mean this statement, because he has no data regarding this writer's reading or studying preferences. As a matter of fact, the writer went through numerous references in relation to this question of "attraction fields," "tension fields," "two-center effect," or whatever term was employed in reference to this phenomenon (*1–9*), and he holds views on the sequence of events in the development of the mechanism identical with those expressed by Dr. Weiss. In fact, once discovered in the literature, both German and English, the writings of Dr. Weiss were placed at the top of the list as a "must." Although, unfortunately, not all the journals have always been available, most of his articles dealing specifically with this subject were studied and thoroughly enjoyed.

Certainly the term "attraction field" does not completely describe the phenomenon, but neither does the phrase "two-center effect," which the writer does not recall as having been used in the literature. So, rather than employ the dubious practice of coining a new name, the term "attraction field" was used. Judging from the many favorable comments received since the article was published, the majority, including those not entirely familiar with the situation, were not misled by the term employed, and no other misinterpretations developed.

A short article of this nature does not permit lengthy historical reviews of previous work or of the precise techniques employed, and so the description of the development of this complex mechanism was compressed into one or two short sentences. For instance, the sequence of events entailed in the statement "Each tissue explant may be considered to set up a mechanism that acts as a stimulus for the oriented pattern of growth for its own cells, as well as the cells of the other explant that shared in the development of the field" can be superimposed on the more lengthy outline of events tabulated by Dr. Weiss. Certainly the growing explants induce syneresis of the fibrin matrix which, in turn, produces tension that reaches its maximum in the common axis between the explants, thus establishing a preferred and oriented pathway for the proliferating cells of both explants. No other explanation was considered, and no inferences were made to a possible "mutual attraction" or that the cells were "pulled over by traction or lured over by mysterious attractions." These two phrases not only are entirely foreign to the article but definitely distort the purpose of it.

If, as Dr. Weiss claims in his letter, "By no means are they pulled over by traction or lured over by mysterious 'attractions'," why do we read in his fascinating chapter on "Differential Growth" (*10*), under the topic of "Orientation of Growth," in which the orientation of growth between two centers of contraction is discussed, the following statements (p. 176):

> By its radial orientations such a contraction pattern can evidently guide peripheral cells toward the center. This is one of the major mechanisms by which cells *are drawn* toward distant destinations, as if "*attracted.*" [And in the next paragraph], tension is not the only agent capable of orienting tissue structure. Any other physical force that is capable of affecting the orientation and aggregation of polar molecules (electrostatic fields, electrophoresis, streaming, etc.) may have comparable effects.

It was specifically this section of the chapter that made this writer especially cautious and on guard when he drafted the recently published article, so as not to include words or phrases that could be misinterpreted and that would present impressions for which he had no data. And nowhere in the article was it intimated that this was a new discovery of the phenomenon. That was clarified in the first paragraph.

Undue credit is given this author for demonstrating the phenomenon by polarized light. This technique was obtained from previous publications (*6, 7*).

The sole purpose of the article was to show the relationship of the distance between the explants to the frequency of the development of "attraction fields" or "two-center effects." The criticism of the analysis of the data by Dr. Weiss was more than welcome, as was his agreement that the quantitative evaluation of the figures of observed incidence expresses the general predictable decline of the "two-center effect" with distance, and that this is a welcome addition to our knowledge.

ALLAN A. KATZBERG
Department of Histology and Embryology
The University of Oklahoma, Oklahoma City

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Root-Grafting in Tropical Trees

YEARS ago I wrote a paper (*Am. J. Botany*, **21**, 121 [1934]) calling attention to the enormous frequency of natural root grafts in *Pinus strobus, P. resinosa,* and *Thuja occidentalis.* Since then I have noted an almost equal amount of root-grafting in *Acer saccharum* and *Ulmus americana,* and a great deal in many other genera. Kuntz and Riker (*Wisconsin Agri. Exp. Sta. Bull. 9* [1950]) have shown that there are enough root grafts in oaks to allow rapid dissemination of oak-wilt disease through them.

Recently, on the grounds of the Federal Experiment Station at Mayagüez, Puerto Rico, and in the surrounding region, I noted the great amount of grafting in the roots of the mango, *Mangifera indica,* which is very common along the roadsides. Soil wash and road cuts have exposed the roots of thousands of these trees.

Ficus nitida, which is rather commonly planted, also shows thousands of grafts for every tree. Of course, the genus *Ficus* is noted for root production and root-grafting, and the development of strangling figs, so notable a feature of tropical forests, depends on the ready grafting of roots and branches that soon encase the supporting tree in a complete wooden jacket from which there is no escape. Members of the Clusiaceae as well, though not figs, are stranglers and show the same ease of grafting as the figs themselves.

After I had seen the condition of the mango roots, I looked for natural grafts in all of the exposed roots I could find (Table 1).

TABLE 1

Genus	Family	Genus	Family
Albizzia	Leguminoseae	*Inga*	Leguminoseae
Aleurites	Euphorbiaceae	*Mangifera*	Anacardiaceae
Antonia	Clusiaceae	*Manihot*	Euphorbiaceae
Artocarpus	Moraceae	*Maximiliana*	Bixaceae
Casuarina	Casuarinaceae	*Nephelium*	Sapindaceae
Cecropia	Moraceae	*Ochroma*	Bombacaceae
Ceiba	Bombacaceae	*Parkeria*	Leguminoseae
Citrus	Rutaceae	*Delonix*	"
Coffea	Rubiaceae	*Posogueria*	Rubiaceae
Couroupita	Lecythidaceae	*Pterocarpus*	Leguminoseae
Diospyros	Ebenaceae	*Sapindus*	Sapindaceae
Enterolobium	Leguminoseae	*Spathodea*	Bignoniaceae
Swietenia	Meliaceae		
Erythrina	"	*Tabebuia*	Bignoniaceae
Euphoria	Sapindaceae	*Tectona*	Verbenaceae
Ficus	Moraceae	*Terminalia*	Terminaliaceae
Genipa	Rubiaceae	*Triplaris*	Polygonaceae
Hura	Euphorbiaceae		

In a cursory examination, root grafts were found in 34 genera belonging to 18 different families. Grafts were seen on trees of a number of genera that I could not identify, and many known genera did not show root exposure enough to determine whether root grafts were present. From my observations I conclude that root-grafting is common in tropical trees—perhaps more common than in those of temperate regions.

CARL D. LARUE
Department of Botany, University of Michigan

Separation of Free-Living Cells

DR. NORTHCRAFT'S ingenious use of ammonium oxalate to separate free-living cells from carrot tissue culture provides workers in this field with a valuable tool with which to attack the problem of single cell division (SCIENCE, **113**, 407 [1951]). The difficulties he records in obtaining an effective but noninjurious concentration reminded me of similar difficulties that I encountered during certain experiments with ammonium oxalate, to bring about chemical changes in the epidermal cell walls of living cabbage roots (*New Phytologist*, **34**, 30 [1935]). It would be interesting if workers with tissue cultures could cause the separated cells to form a solid tissue again. In this connection I suggest replacing the ammonium oxalate in the culture medium by a slightly alkaline solution of a calcium salt.

ROBERT G. H. CORMACK
Department of Botany, University of Alberta

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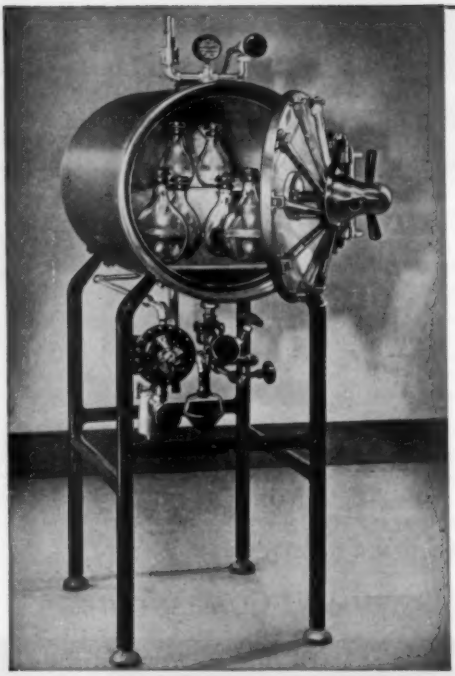

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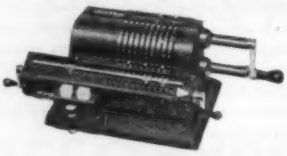

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Mar. 20–21. Conference on Cooling of Airborne Electronic Equipment. Ohio State University, Columbus.
Mar. 24–27. Ergonomics Society Symposium on Fatigue. Cranfield, Bucks, Eng.
Mar. 25–27. CIBA Foundation Colloquium on Endocrinology. London.
Mar. 28–29. Eastern Psychological Association. Chalfonte-Haddon Hall, Atlantic City.
Mar. 29–30. American Psychosomatic Society (Annual). Chicago.
Mar. 31. Technical Societies Council of New Jersey (Annual). Essex House, Newark.
Mar. 31–Apr. 2. Mid-West Gas Association (Annual). Hotel Radisson, Minneapolis.
Mar. 31–Apr. 3. American Chemical Society. Milwaukee, Wis.
Mar. 31–Apr. 4. American Congress on Obstetrics and Gynecology. Netherland Plaza Hotel, Cincinnati.
Mar. 31–Apr. 4. Symposium on the Suprarenal Cortex. Colston Research Society. Bristol, Eng.
Apr. 3–8. The Physical Society (Annual). Exhibition of Scientific Instruments and Apparatus. Royal College of Science, London.
Apr. 4–5. History of Science Society. Brown University, Providence, R. I.
Apr. 4–5. National Aviation Education Council. Cooley Plaza Hotel, Boston.
Apr. 5. Association for Research in Ophthalmology, Midwestern Section (Annual). Indiana University Medical Center, Indianapolis.
Apr. 5–6. Eastern Sociological Society (Annual). Haverford College, Haverford, Pa.
Apr. 5–9. American Association of School Administrators (Regional). Boston.
Apr. 6–9. American College of Allergists (Annual). William Penn Hotel, Pittsburgh.
Apr. 6–9. National Agricultural Chemicals Association. Fairmont Hotel, San Francisco.
Apr. 7–8. Histochemical Society. Hotel New Yorker, New York.
Apr. 7–9. American Society of Lubrication Engineers (Annual). Hotel Statler, Cleveland.
Apr. 7–9. Seminar on International Wool Research Project. Lowell Textile Institute, Lowell, Mass.
Apr. 8–10. Faraday Society Discussion. Leeds, Yorkshire, Eng.
Apr. 9. International Association of Medical Museums. Hotel New Yorker, New York.
Apr. 10–12. American Association of Pathologists and Bacteriologists (Annual). Hotel New Yorker, New York.
Apr. 10–15. American Society of Ichthyologists and Herpetologists (Annual). University of Texas, Austin.
Apr. 11–12. Montana Academy of Sciences (Annual). Bozeman.
Apr. 14–18. American Physiological Society. New York.
Apr. 14–18. American Society of Biological Chemists (Annual). Hotel New Yorker, New York.
Apr. 14–18. American Society for Pharmacology and Experimental Therapeutics. Hotel Statler, New York.
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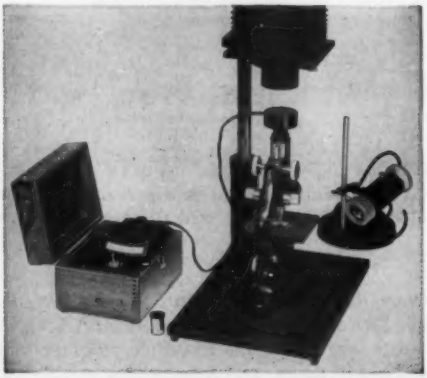

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Publications Received

Biology of the White Crappie in Illinois. Bull. Vol. 25, Art. 4. Donald F. Hansen. Aug. 1951. Pp. 211–265. Illus.; ***Commercial and Sport Fishes of the Mississippi River between Caruthersville, Mo., and Dubuque, Iowa.*** Bull. Vol. 25, Art. 5. Paul G. Barnickol and William C. Starrett. Sept. 1951. Pp. 267–350. Illus.; ***Commercial Fisheries of Illinois Rivers: A Statistical Report for 1950.*** Biological Notes No. 25. William C. Starrett and Sam A. Parr. Nov. 1951. 35 pp. Illus.; ***Lead Poisoning in Wild Waterfowl.*** Biological Notes No. 26. James S. Jordan and Frank C. Bellrose. Urbana: Illinois Natural History Survey Div., Dec. 1951. 27 pp. Illus.

Birds from Liberia. Fieldiana: ***Zoology,*** Vol. 32, No. 9. Austin L. Rand. $1.00; ***Late Devonian Fresh-Water Fishes from the Western United States.*** Fieldiana: ***Geology,*** Vol. 11, No. 5. Robert H. Denison. Illus. 75¢; ***A Revision of the North American and European Staphylinid Beetles of the Subtribe Gyrophaenae (Aleocharinae, Bolitocharini).*** Fieldiana: ***Zoology,*** Vol. 32, No. 10. Charles H. Seevers. Illus. $1.25; ***The Truth About Snake Stories.*** Popular Ser. Zool., No. 10. Karl P. Schmidt. Chicago: Chicago Nat. History Museum, 1951. 23 pp. Illus. 20¢.

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Insecticidal Control of Cabbage Pests: Canberra 1944–48. CSIRO Bull. No. 258. T. Greaves and D. G. Venables. 51 pp., 5 plates. 1950; ***Adjuvants for Pyrethrins in Fly Sprays.*** CSIRO Bull. No. 261. R. W. Kerr. 63 pp. 3 plates; ***Third Annual Report, 1950–1951.*** Melbourne: Commonwealth Scientific and Industrial Research Organization, Australia, 1951.

David Starr Jordan, A Bibliography of His Writings, 1871–1931. Stanford Univ. Pubs., Univ. Ser., Library Studies Vol. 1. Compiled by Alice N. Hays. xiii + 195 pp. Paper, $4.00; ***The "Prestige Papers:" A Survey of their Editorials.*** Series C, Symbol Study No. 2, Hoover Inst. Studies. Ithiel de Sola Pool. Stanford, Calif.: Stanford Univ. Press, 1952. vii + 146 pp. Paper, $1.75.

Medical Center. Eighty-third Annual Report of The Presbyterian Hospital at the Columbia-Presbyterian Medical Center. New York: The Presbyterian Hospital, 1951.

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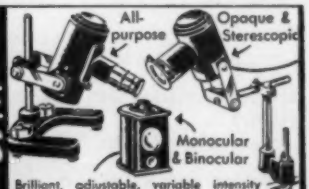

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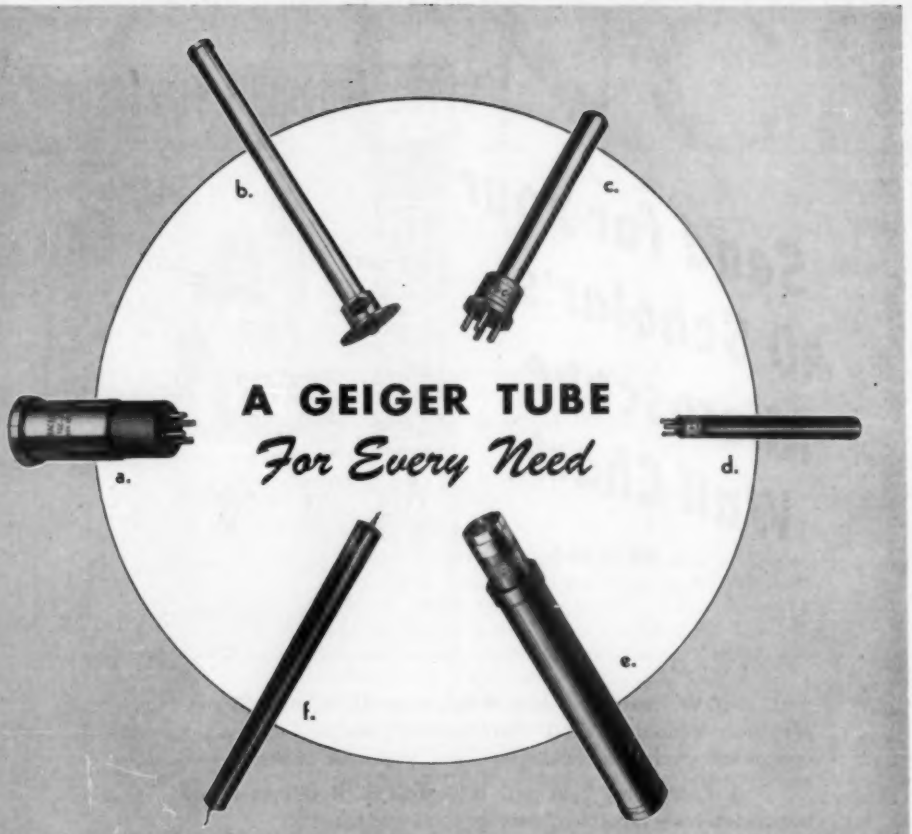

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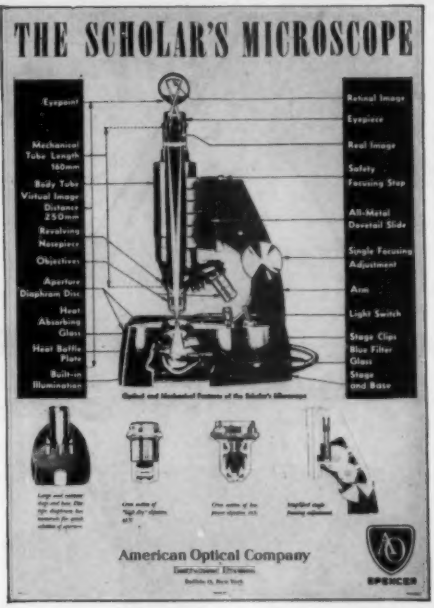

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